

# Nutraceuticals: Dietary Flavonoids

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Flavonoids include many of the most common plant pigments. They are consumed as part of the human diet. Flavonoids can be divided into several classes depending on their structure. They are responsible for much of the flavor and color of fruits and vegetables. The flavones and flavonols give yellow or orange colors, the anthocyanins red, violet or blue colors. The aurones are golden yellow pigments while flavanones and flavanonols are either colorless or only slightly yellow.

This mini review highlights the sources of dietary flavonoids, their bioactivities, and their mechanisms of actions. Dietary flavonoids provide both health (nutrition) and medical (pharmaceutical) benefits. Dietary flavonoids are preventives or prophylactics rather than therapeutics. The flavonoids are just one of the many classes of nutraceuticals present in our diet.

## Dietary Flavonoids Sources and Uses

Common flavan-3-ols present in fresh fruits, vegetables, and nuts are catechin, catechin gallate, epicatechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, galocatechin, and galocatechin gallate (Harnly et al., 2006). Dietary flavonoids also include the anthocyanins cyanidin, delphinidin, malvidin, pelargonidin, peonidin and petunidin together with the flavanones hesperetin and naringenin, the flavones apigenin and luteolin, and the flavonols myricetin, kaempferol, and quercetin.

Quercetin is the most abundant flavonol. It is present in black and green teas, onions, apples, grapes, beans (Somerset & Johannot, 2008), broccoli (Vasanthi et al., 2009), lettuce (Ribas-Agusti et al., 2011), berries (Harnly et al., 2006), oregano (Mueller et al., 2008), mangoes (Wilkinson et al., 2008), and tomatoes (Slimestad et al., 2008), among others. Yellow and red onion bulbs

contain 270-1187 and 415-1917mg flavonols mg/kg fresh weight, respectively, as well as anthocyanins (39-240 mg/kg fresh weight) and dihydroflavonols (Slimestad et al., (2007)). Berries are also rich in anthocyanins while black and green teas are also sources of flavan-3-ols (Somerset & Johannot, 2008). Citrus fruits contain flavanones. Coffee contains myricetin. The major flavone sources are parley, celery, and English spinach while the major anthocyanidin source is wine. Tea, legumes, and wines contributed to 48% of daily intake of proanthocyanidins (Wang et al., 2011). Durian, pomelo, guava, and ripe banana are good sources of flavonoids (Kongkachuichai et al., 2010). Differences in cultivars and growing conditions may lead to differences in the relative amounts of dietary flavonoids.

Natural food-derived flavonoids may help reduce the incidence of atherosclerosis (Terao, 2009), cancer (Gibellini et al., 2011; Mishra et al., 2011; Clere et al., 2011; Nishiumi et al., 2011; Yao et al., 2011), cardiovascular diseases (Bojic et al., 2011, Hubbard et al., 2006), diabetes (Zheng et al., 2011), thrombosis (Phang et al., 2011), inflammation in arthritis, asthma, encephalomyelitis, and atherosclerosis (Gonzalez et al., 2011), neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (Mandel et al., 2011; Craggs & Kalaria, 2011), obesity (Birari et al., 2011; Bell et al., 2011), hyperlipidemia (Wang et al., 2011), nerve injury (Jager & Saaby, 2011), and hypertension (Cassidy et al., 2011).

## *In Vitro* Studies and Animal Models

Apples contain high levels of flavonols, catechins, and oligomeric procyanidins. Red apples are rich in anthocyanidins. Apple extracts prevented skin, mammary and colon cancers in animal models (Gerhauser, 2008). Apple extracts also exhibited anti-

inflammatory activity (Lauren et al., 2009). Red wine, which is rich in anthocyanins and flavonoids, inhibited the growth of human breast cancer cells (MCF-7) with relatively low cytotoxicity towards normal human mammary epithelial cells and a non-tumorigenic MCF-10A cell line (Hakimuddin et al., 2004). Broccoli provided anti-oxidants, regulated enzymes and controlled apoptosis and cell cycle (Vasanthi et al., 2009).

Flavored black teas, with higher levels of catechins, quercetin, and rutin, showed stronger anti-oxidant activity than fruit teas, which contained higher levels of naringin and hesperidin (Pekal et al., 2011). Bananas also showed antioxidant activity against rats fed normal as well as high fat diets (Vijayakumar et al., 2008). The concentrations of peroxidation products were significantly decreased whereas the activities of catalase, superoxide dismutase, and glutathione were significantly enhanced. The antioxidant activity of strawberry against PC12 cells, a model system for neuronal differentiation, treated with hydrogen peroxide was higher than banana and orange. The reduction of oxidative stress-induced neurotoxicity and the higher neuroprotective activity of strawberry may be due to its higher anthocyanins content compared to banana and orange (Heo & Lee, 2005).

Fruits and vegetables rich in anthocyanins, such as strawberry, raspberry and red plum, were potent anti-oxidants, followed by those rich in flavanones, such as orange and grapefruit, and flavonols, present in onion, leek, spinach and green cabbage, while the hydroxycinnamate-rich apple, tomato, pear and peach consistently elicited lower antioxidant activities. *The antioxidant activities (TEAC) in terms of 100 g fresh weight uncooked portion size were in the order: strawberry >> raspberry = red plum >> red cabbage >>> grapefruit = orange > spinach > broccoli > green grape e" onion > green cabbage > pea > apple > cauliflower > tomato e" peach=leek > banana e" lettuce* (Proteggente et al., 2002).

Quercetin inhibited the growth of several human cancer cell lines at different phases of the cell cycle by direct pro-apoptosis with almost total absence of damage for normal, non-transformed cells (Gibellini et al., 2011). Quercetin also inhibited the activation of peroxisome

proliferator-activated receptor isoforms (PPARs) alpha, beta and gamma (Wilkinson et al., 2008). PPARs are drug targets in metabolic syndrome, wherein obesity, hyperglycemia, hypertension, and hyper/dyslipidemia are all present (Mueller et al., 2008). Quercetin and myricetin blocked the genotoxic effects of some cooked-food mutagens (Alldrick et al., 1986). The most potent anti-aggregatory activity was shown by 3,6-dihydroxyflavone and syringetin (Bojic et al., 2011). Luteolin was more cytotoxic than apigenin against human chronic myelogenous erythroleukemia (K562) and bladder carcinoma (RT112), mainly due to induction of apoptosis (Kilani-Jaziri et al., 2011). Apigenin was able to induce apoptosis in human chronic lymphocytic leukemia (Eheb) cell line (Hashemi et al., 2010). Apigenin, epigallocatechin gallate, delphinidin and genistein appear to be beneficial compounds in various stages of carcinogenesis (Clere et al., 2011). Genistein, an isoflavone present in soy, prevents breast, prostate, and colon cancer (Ullah et al., 2011).

### Epidemiological Studies

Several population-based studies suggested that intake of dietary flavonoids is associated with health. In The Netherlands, the average intake of dietary flavonoids is 23 mg/day. The important sources of dietary flavonoids were tea, onions, and apples (Hertog et al., 1993). Tea was also the main dietary source of flavonoids in the UK but this tea-drinking population has a high incidence of colorectal cancer (Kyle et al., 2010). Results of a population-based case-control study showed that non-tea quercetin reduced the incidence of colon but not rectal cancer. In the Rotterdam study, tea drinkers showed a lower relative risk of incident myocardial infarction (Geleijnse et al., 2002) while in the Zutphen study, habitual intake of dietary flavonoids, with tea as major source, protected them against stroke (Keli et al., 1996).

In a double-blind randomized cross-over study, ingestion of onion soup inhibited collagen-stimulated platelet aggregation, which may lead to reduced risk of thrombosis and potential cardiovascular disease (Hubbard et al., 2006). In a study of Japanese women, their high intake of flavonoids and isoflavones, whose major sources are onions and tofu, respectively, led to

low plasma total cholesterol and plasma low density lipoprotein (LDL) cholesterol concentrations, which may explain the low incidence of coronary heart disease among Japanese women (Arai et al., 2000). Populations with high intake of isoflavones through soy consumption have lower incidence of breast, prostate, and colon cancers (Ullah et al., 2011). Among the Finnish population, intake of apples, the major source of quercetin, decreased the relative risk of thrombotic or embolic stroke but quercetin intake was not associated with the incidence of cardiovascular disease (Knekt et al., 2000). A cross-sectional study of U.S. women showed that intake of flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins, and polymeric flavonoids led to modestly lower concentrations of inflammatory and endothelia dysfunction markers (Landberg et al., 2011).

Prospective epidemiologic studies and several short term controlled randomised clinical trials have shown that consumption of some foods or beverages with high flavonoid content, especially flavanols and anthocyanins, lowered the incidence of coronary stroke mortality or prevalence of neurodegenerative diseases including Alzheimer's and Parkinson's diseases (Stoclet & Schini-Kerth, 2011). Samples tested were red wine, some grape juices, red fruits, tea, and cocoa. Black tea and green tea catechins also protected the aging brain and reduce the incidence of dementia and neurodegenerative diseases (Mandel et al., 2011).

Results of a cross-sectional survey of participants, with known childhood intelligence quotients (IQ), who carried out various neuropsychological tests at age 70 did not show a relationship between flavonoids intake and the prevention of cognitive decline. *Total fruit, citrus fruits, apple and tea intakes were initially found to be associated with better scores in a variety of cognitive tests, but the associations were no longer statistically significant after adjusting for confounding factors, including childhood IQ* (Butchart et al., 2011).

A four-year intervention study on adenoma recurrence of colorectal cancers showed that interleukin single nucleotide polymorphisms (IL SNPs), in combination with a flavonol-rich diet or decreased serum IL, lowered

the risk of adenoma recurrence (Bobe et al., 2011). In an observational osteoporosis study of peri-menopausal Scottish women, their mean dietary flavonoid intake was  $307 \pm 199$  mg/d with catechins contributing the most to flavonoid intakes (55%). *Annual % change in bone mineral density was associated with intakes of procyanidins and catechins, and flavanones were negatively associated with bone resorption markers* (Hardcastle et al., 2010). In a prospective study, the habitual intake of flavonoids by participants was associated with hypertension. During 14 years of follow-up, it was established that anthocyanins, some flavone and flavan-3-ol compounds showed vasodilatory activities and may contribute to the prevention of hypertension (Cassidy et al., 2011).

### Mechanisms of Action

The anti-carcinogenic effects of dietary flavonoids may be due to their antagonistic effect on the aryl hydrocarbon receptor (AhR), and regulation of phase I and II drug metabolizing enzymes and phase III transporters. Dietary flavonoids also modulated cell signal transduction pathways (Nishiumi et al., 2011) related to cellular proliferation, apoptosis, and angiogenesis (Yao et al., 2011) in various tumor cells and animal models (Shanmugam et al., 2011) as well as pro-inflammatory and oncogenic signals (Fraga and Oteiza, 2011). Apigenin increased the cellular levels of CD26 on HT-29 and HRT-18 human colorectal cancer cells. *CD26 is a multifunctional cell-surface protein that through its associated dipeptidyl peptidase (DPPIV) and ecto-adenosine deaminase (eADA) enzyme activities is able to suppress pathways involved in tumour metastasis* (Lefort&Blay , 2011). Genistein-induced apoptosis is inhibited by reactive oxygen species (ROS) scavengers and by mobilization of endogenous copper, thus disabling a copper specific chelator from inhibiting apoptosis (Ullah et al., 2011).

Some dietary flavonoids modified protein kinases mediated signal transmission inducing antioxidant and anti-inflammatory genes expression and inhibiting oxidant and inflammatory gene expression (Stoclet & Schini-Kerth, 2011). Molecular targets, such as cyclooxygenase and lipoxygenase, and cellular targets, such as macrophages, lymphocytes, epithelial cells, and

endothelium, have been used in identifying the mechanism of anti-inflammatory activity. Flavonoids, despite their structural differences, consistently inhibited NF- $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling and down-regulated the expression of pro-inflammatory markers in myeloid cells (Gonzalez et al., 2011). Assessment of the anti-inflammatory mechanism of action of flavonoids showed that citrus fruits were modestly associated with lower plasma IL-18 concentrations while higher intake of grapefruit was significantly related with lower concentrations of plasma C-reactive protein (CRP) and soluble tumor necrosis factor receptor-2 (sTNF-R2) (Landberg et al., 2011).

In the central nervous system, several flavones bind to the benzodiazepine site on the GABA(A)-receptor resulting in sedation, anxiolytic or anti-convulsive effects. Flavonoids also inhibited monoamine oxidase A or B and functioned as anti-depressants, which may improve the symptoms of Parkinson's disease (Jager & Saaby, 2011). The neuroprotective effects of green tea catechins may be due to their ability to modulate intracellular neuronal signaling and metabolism, cell survival/death genes, and mitochondrial function as well as their anti-oxidant activity (Mandel et al., 2011).

Rats fed with a diet containing 0.5% quercetin showed a relative increase in the levels of lactate, low-density lipoprotein/very low-density lipoprotein (LDL/VLDL), and serum low-density lipoprotein cholesterol (LDL-C) and a relative decrease in glucose, high-density lipoprotein (HDL), and some amino acids (Zhao et al., 2011). Biochemical measurements confirmed that the serum level was increased significantly after quercetin treatment, indicating that quercetin can induce a remarkable change in cholesterol metabolism.

Flavonoids also acted on reactive oxygen species (ROS) (Yao et al., 2011). Dietary flavonoids may directly scavenge or quench ROS as well as inhibit oxidative enzymes that generate these ROS (Terao, 2009). Antioxidants are capable of preventing ROS-induced oxidative damage or oxidative stress, which contributes to the initiation and progression of several chronic diseases. Prevention of the formation and reaction of ROS by antioxidants decreased the risk of major

diseases. *For example, the oxidation of low density lipoprotein (LDL) cholesterol yields a product that damages the vascular system. Thus, a lower intake of saturated fats to decrease the levels of LDL cholesterol, together with an adequate intake of antioxidants, is the optimal approach to lower heart disease risk* (Weisburger 1999). Direct-acting carcinogens and their formation are inhibited by antioxidants. The growth, cell proliferation and development of abnormal preneoplastic and neoplastic cells are also prevented by antioxidants. Even the ageing process is slowed down by antioxidants.

### **Metabolism of dietary flavonoids**

Flavonoids are found in plants as glycosides. Before oral absorption, flavonoids undergo deglycosylation either by lactase phloridzin hydrolase or cytosolic  $\alpha$ -glucosidase. The absorbed aglycone is then conjugated (Jager & Saaby, 2011) forming glucuronide, methyl, and sulphate derivatives, which may have different bioactivities than the parent flavonoid. In simulated gastric digestion, anthocyanin glycosides remained stable but their aglycones were significantly degraded. During subsequent pancreatic/intestinal digestion only pelargonidin-3-glucoside remained stable while cyanidin-3-glucoside, cyanidin, and pelargonidin aglycones were completely degraded. After microsomal metabolism, pelargonidin formed 4-hydroxybenzoic acid, which was metabolized to form two additional glucuronide conjugates, while cyanidin formed protocatechic acid, which was further metabolized to form three glucuronide conjugates (Woodward, et al., 2011).

Methyl derivatives of quercetin, 3'-O-methyl-quercetin and 4'-O-methyl-quercetin, exhibited anti-inflammatory activity by blocking the expression of intercellular adhesion molecule-1 (ICAM-1) while quercetin-3-O-glucuronide, quercetin-3'-O-sulfate, and phenolic acid metabolites of quercetin did not inhibit adhesion molecule expression. 4',4''-Di-O-methyl-epigallocatechin-3-O-gallate (EGCG) inhibited ICAM-1 expression but EGCG and 4''-O-methyl-EGCG had no effect (Lotito et al., 2011). Cooking reduced antioxidant activity and phenolic content (Kuti and Konuru, 2004).

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