Health Benefits of Dietary Flavonoids: Flavonols and Flavones

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There is increasingly convincing evidence from in vitro, in vivo and epidemiological studies suggesting the benefits of flavonoids in fruits and vegetables in the prevention of chronic diseases because of their antioxidant, anti-cancer, and cardiovascular-protective effects.

Flavonoids are a group of phenolic compounds that have been identified in fruits, vegetables and other plant foods, and have been linked to reducing the risk of major chronic diseases. More than 4,000 distinct flavonoids have been identified, but many are still unknown and need to be identified before we can fully understand the health benefits of phytochemicals. More and more convincing evidence suggests that the benefits of phytochemicals in fruits and vegetables may be even greater than currently understood because oxidative stress induced by free radicals is involved in the etiology of a wide range of chronic diseases.

Flavonoids commonly have a generic structure consisting of two aromatic rings (A and B rings) linked by three carbons that are usually in an oxygenated heterocycle ring, or C ring (Figure 1). Differences in the generic structure of the heterocycle C ring classify them as flavonols, flavones, flavanols (catechins), flavanones, anthocyanidins, and isoflavonoids. Flavonols (quercetin, kaempferol, and myricetin) and flavones (luteolin and apigenin) are common flavonoids in the daily diet (Fig. 1, Table 1).

Flavonoids are most frequently found in nature as glycosides, but can occur as aglycones, especially due to the effects of food processing. Many different glycosides can be found in nature as more than 80 different sugars have been discovered bound to flavonoids.

Bioavailability

Human intake of all flavonoids is estimated at a few hundred milligrams (Hollman and Katan, 1999) to 650 mg per day (Kuhnau, 1976). The total average intake of flavonols (quercetin, myricetin, kaempferol) and flavones (luteolin, apigenin) was 23 mg/day, of which quercetin contributed about 70 percent, kaempferol 17 percent, myricetin 6 percent, luteolin 4 percent and apigenin 3 percent (Hertog et al, 1993). In this study, tea was the major source of flavonols and flavones at 48 percent of total intake, followed by onions at 29 percent, and apples at 7 percent. Flavonoids are usually bound in foods to sugars as beta-glycosides and were considered non-absorbable. Human absorption was greater than was initially thought. Hollman et al. (1995) fed nine ileostomy patients, who lack colons, a single dose of quercetin in onions, which contain mostly quercetin-3-glucoside; pure quercetin-3-rutinoside (rutin), the predominant form of quercetin in tea; and pure quercetin aglycone. The average absorption of quercetin was 52 percent from onions, 17 percent for quercetin-3-rutinoside, and 24 percent for quercetin aglycone. Because the quercetin 3-glucoside present in onions cannot be cleaved by digestive enzymes, it was transported intact into the enterocyte by a sodium-dependent glucose transporter. The same group later fed nine subjects quercetin as a single large dose through onions (quercetin glucoside), apples (both glucose or non-glucose quercetin glycosides), and pure quercetin-3-rutinoside, and monitored plasma quercetin levels over 36 hours (Hollman et al. 1997). Quercetin from onions was absorbed most rapidly, and rutin least rapidly, indicating that quercetin glucoside is likely absorbed from the stomach or small intestine, while quercetin from rutin is probably absorbed from the colon after microbial cleavage of the sugar. Peak time and peak plasma levels were 0.7 h and 224 ng/mL after the onion meal, 2.5 h and 92 ng/mL after the apples, and 9 h and 90 ng/mL after the quercetin-3-rutinoside. Bioavailability of quercetin from apples and pure quercetin-3-rutinoside (rutin) was 30 percent of that from onions. Half-life of quercetin in plasma was about 24 hours, suggesting that accumulation of the compound is possible. In a recent study, six subjects were fed a meal containing fried onions

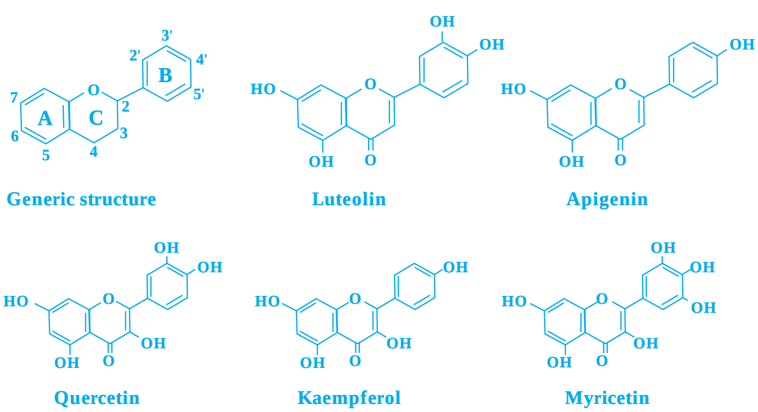

Figure 1. The generic structure of flavonoids, and structures of common flavonols and flavones.

and fresh cherry tomatoes (Boyle et al. 2000). Plasma quercetin levels increased from 16.5 ± 2.7 ng / mL to 104.9 ± 10.42 ng / mL four hours after ingestion and remained elevated at eight hours. After 24 hours, plasma quercetin levels were still higher than the baseline. Therefore, the sugar moiety is important for flavonoid absorption and bioavailability, and conjugation with glucose enhances bioavailability.

TABLE 1

Major food sources of flavonols and flavones

Flavonoids		Major Food Sources
Flavonols	Quercetin	Onion, apple, broccoli, cranberry, grape, red wine*
	Kaempferol	Kale, broccoli, parsley, leek, apple, berries, tea
	Myricetin	Parsley, cranberry, grape, red wine, berries, spinach
Flavones	Luteolin	Celery, green pepper, spinach, green bean
	Apigenin	Celery, parsley, apple, grape, leek, onion

* Listed in order of content in foods (Arai et al, 2000; Hertog et al, 1993; Hollman and Arts, 2000).

Effects of Processing and Storage

The effect of processing on flavonoids depends on the type of food, class of flavonoids being evaluated, and processing and storage conditions. Flavonoids are usually present in foods as conjugates in glycosylated or esterified forms. Different processing techniques may affect flavonoid release from the bound. The effects of heat treatments on quercetin and kaempferol levels in onions, green beans, and peas have been studied (Ewald et al. 1999). Pre-processing of onions (peeling, trimming, and chopping) prior to blanching caused the greatest loss (39 percent) in flavonoids. Subsequent cooking, frying or warm-holding for up to 2 h of the blanched vegetables, resulted in insignificant losses, with kaempferol showing a higher loss compared to quercetin.

In studying the effects of domestic processing and storage on quercetin, myricetin, and kaempferol in five berries, Hakkinen et al. (2000) reported that cooking strawberries with sugar to make jam resulted in minor losses (quercetin 15 percent, kaempferol 18 percent), while a 40 percent quercetin loss occurred during cooking of bilberries with water and sugar to make soup. Cold-pressing was better than steam-extraction in extracting flavonols from black currants. When stored at -20˚C for nine months, quercetin content decreased (40 percent) in bilberries and lingonberries, but not in black currants or red raspberries. Under similar conditions, myricetin and kaempferol were more susceptible to losses (Hakkinen et al. 2000). Exposure of lettuce leaf to light after shredding produced significant losses of flavonoid moieties in green oak leaf (94 percent), green batavia (25 percent), iceberg (36 percent), lollo biondo (24 percent), red oak leaf (43 percent) and lollo rosso (6 percent) samples (DuPout et al, 2000). Storage of lettuce and endive heads in the dark at 1˚C and 98 percent humidity for seven days also caused losses of total flavonol glycosides in the range of 7-46 percent (Dupont et al, 2000). Kaempferol conjugates, including kaempferol 3-O-glucoside, kaempferol 3-O-glucuronide, and kaempferol 3-O-(6-O-malonyl) glucoside have been found in endive varieties. Analysis of kaempferol levels in nine berries before and after they were used for jam preparation indicated that fresh and jam samples did not change much, indicating the effect of jam processing was little (Amakura et al, 2000). However, the effect of processing on the bioavailability of flavonoids has not been investigated.

Health Benefits

More and more convincing evidence from in vitro, in vivo and epidemiological studies suggests the benefits of flavonoids in fruits and vegetables in the prevention of chronic diseases is because of their antioxidant, anti-cancer, and cardiovascular-protective effects.

Cancer*:* Evidence suggests that dietary antioxidants can reduce cancer risk. Block et al. (1992) established this in an epidemiological review of approximately 200 studies that examined the relationship between fruit and vegetable intake and cancers of the lung, colon, breast, cervix, esophagus, oral cavity, stomach, bladder, pancreas and ovary. In 128 of 156 dietary studies, the consumption of fruits and vegetables was found to have a significant protective effect. In persons whose intake of fruits and vegetables was low compared to those with high intake, the risk of cancer was twice as much. Significant protection was found in 24 of 25 studies for lung cancer. Fruits were significantly protective in cancers of the esophagus, oral cavity, and larynx. In 26 of 30 studies, there was a protective effect of fruit and vegetable intake in respect to cancers of the pancreas and stomach and in 23 of 38 studies for colorectal and bladder cancers. A prospective study involving 9,959 men and women at ages 15-99 in Finland showed an inverse association between the intake of flavonoids and incidence of all sites of cancer combined (Knekt et al, 1997). After a 24-year follow-up, the risk of lung cancer was reduced to 50 percent in the highest quartile of flavonol intake. Consumption of quercetin in onions and apples was found to be inversely associated with lung cancer risk in Hawaii (Le Marchand et al. 2000). The effect of onions was particularly strong against squamous cell carcinoma. Boyle et al. (2000) showed that increased plasma levels of quercetin following a meal of onions was accompanied by increased resistance to strand breakage by lymphocyte DNA and decreased levels of some oxidative metabolites in the urine.

Carcinogenesis is a multi-step process and oxidative damage is linked to formation of tumors through several mechanisms. Oxidative stresses induced by free radicals cause DNA damage, and when left unrepaired can lead to base mutation, single and double strand breaks, DNA cross-linking and chromosomal breakage and rearrangement. This potentially cancer-inducing oxidative damage might be prevented or limited by dietary antioxidants found in fruits and vegetables. Studies to date have demonstrated that flavonoids in common fruits and vegetables can have complementary and overlapping mechanisms of actions, including modulation of detoxification enzymes, scavenging oxidative agents, stimulation of the immune system, regulation of gene expression in cell proliferation and apoptosis, hormone metabolism, and antibacterial and antiviral effects.

Cardiovascular disease*:* Dietary flavonoid intake was significantly inversely associated with mortality from coronary heart disease, and an inverse relation (weaker but significant) with incidence of myocardial infarction (Hertog et al, 1993b). In a study in Finland, the intake of apples and onions, both high in quercetin, was inversely correlated with total and coronary mortality (Knekt et al. 1996). In a recent Japanese study, the total intake of flavonoids (quercetin, myricetin, kaempferol, luteolin and ficetin) was inversely correlated with the plasma total cholesterol and low density lipoprotein (LDL) cholesterol concentrations (Arai et al. 2000). As a single phytochemical, quercetin intake was inversely related to total cholesterol and LDL plasma levels.

Mechanisms for the prevention of artheriosclerosis by antioxidants have been proposed. For example, oxidized low-density lipoprotein (LDL) cholesterol is known as the atherogenic factor that contributes to heart disease. Oxidized LDL is typically taken up by macrophage scavenger receptors, thus promoting cholesterol ester accumulation and foam cell formation, which promotes atherosclerotic disease. Dietary antioxidants that are incorporated in LDL are themselves oxidized when these LDL are exposed to prooxidative conditions before any extensive oxidation can occur in the sterol or polyunsaturated fatty acids (Sanchez-Moreno et al., 2000). In addition, phytochemicals have been shown to have roles in reduction of platelet aggregation, modulation of cholesterol synthesis and absorption, and reduction of blood pressure.

Summary

In summary, dietary modifications by increasing the consumption of fruits, vegetables, and whole grains is a practical strategy for consumers to optimize their health and reduce the risk of chronic diseases. It is recommended that consumers follow the USDA / USDHHS Dietary Guidelines to meet their nutrient requirements for health improvement and disease prevention. Antioxidants are best acquired through whole food consumption.

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