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# Flavonoids

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## Summary

- Flavonoids are a large family of polyphenolic compounds synthesized by plants. *(More information)*
- Scientists are interested in the potential health benefits of flavonoids associated with fruit and vegetable-rich diets. *(More information)*
- Many of the biological effects of flavonoids appear to be related to their ability to modulate cell-signaling pathways, rather than their antioxidant activity. *(More information)*
- Although higher intakes of flavonoid-rich foods are associated with reductions in cardiovascular disease

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risk, it is not yet known whether flavonoids themselves are cardioprotective. *(More information)*

- Despite promising results in animal studies, it is not clear whether high flavonoid intakes can help prevent cancer in humans. *(More information)*
- It is not yet clear how flavonoid consumption affects neurodegenerative disease risk in humans. *(More information)*
- Higher intakes of flavonoid-rich foods have been associated with reduced risk of chronic disease in some studies, but it is not known whether isolated flavonoid supplements or extracts will confer the same benefits as flavonoid-rich foods.

## Introduction

Flavonoids are a large family of compounds synthesized by plants that have a common chemical structure (**Figure 1**). Flavonoids may be further divided into subclasses (**Table 1**). Over the past decade, scientists have become increasingly interested in the potential for various dietary flavonoids to explain some of the health benefits associated with fruit- and vegetable-rich diets. This article reviews the scientific evidence for the hypothesis that dietary flavonoids promote health and prevent disease in humans. For more detailed information on the health effects of isoflavones, a subclass of flavonoids with estrogenic activity, see the separate article on Soy Isoflavones. For more information on the health benefits of foods that are rich in flavonoids, see the separate articles on Fruit and Vegetables, Legumes, and Tea.

**Figure 1. Basic Chemical Structure of a Flavonoid**

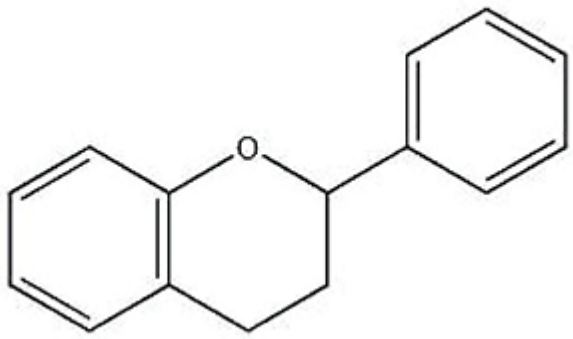
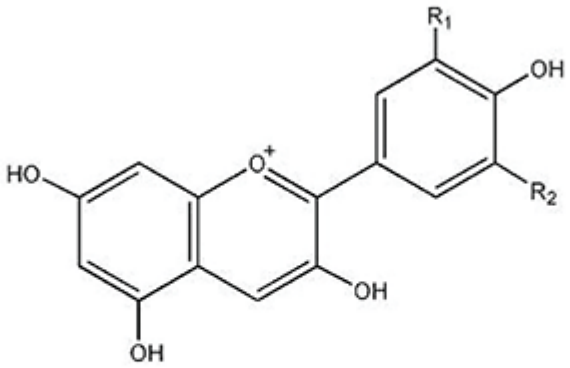



**Table 1. Common Dietary Flavonoids**
**(Select the highlighted text to view chemical structures.)**

| Flavonoid Subclass | Dietary Flavonoids | Some Common Food Sources |
|---|---|---|
| **Anthocyanidins** | Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin | Red, blue, and purple berries; red and purple grapes; red wine |
| **Flavanols** | **Monomers (Catechins)**: Catechin, Epicatechin, Epigallocatechin Epicatechin gallate, Epigallocatechin gallate<br>**Dimers and Polymers**: | **Catechins**: Teas (particularly green and white), chocolate, grapes, berries, apples<br>**Theaflavins, Thearubigins**: Teas |

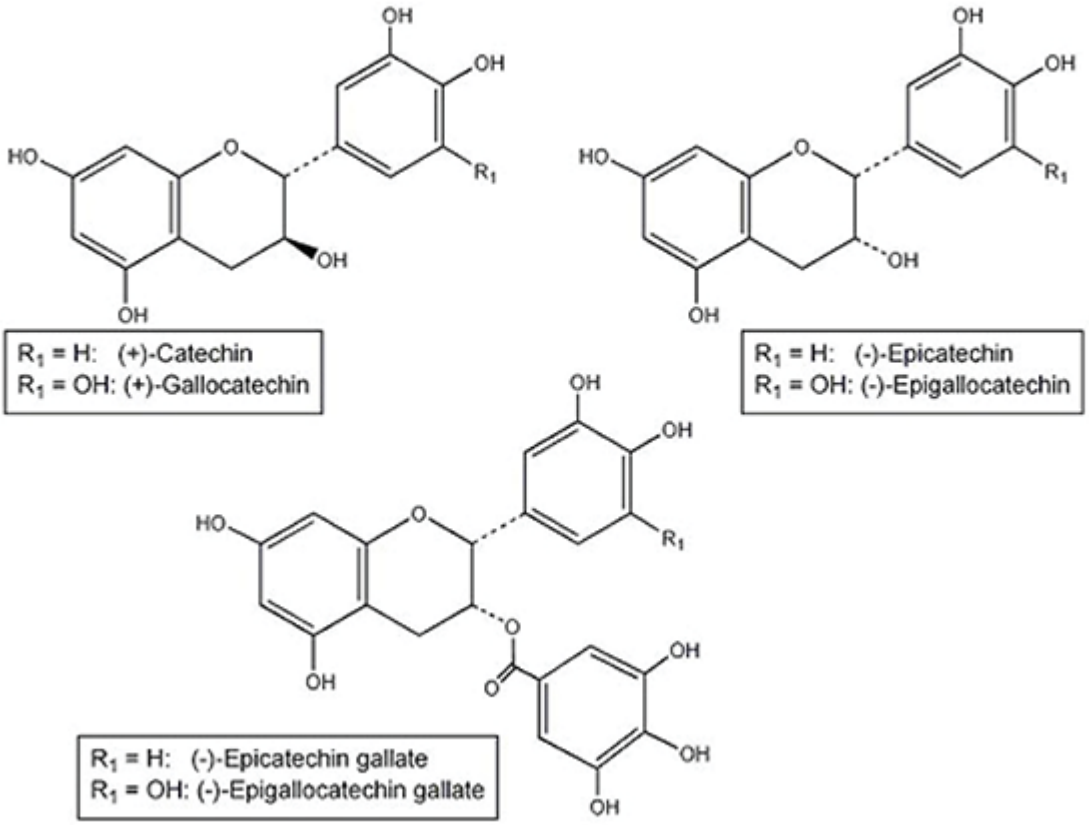
| | | |
|---|---|---|
| | Theaflavins, Thearubigins, Proanthocyanidins | (particularly black and oolong) **Proanthocyanidins**: Chocolate, apples, berries, red grapes, red wine |
| **Flavanones** | Hesperetin, Naringenin, Eriodictyol | Citrus fruit and juices, e.g., oranges, grapefruit, lemons |
| **Flavonols** | Quercetin, Kaempferol, Myricetin, Isorhamnetin | Widely distributed: yellow onions, scallions, kale, broccoli, apples, berries, teas |
| **Flavones** | Apigenin, Luteolin | Parsley, thyme, celery, hot peppers, |
| **Isoflavones** | Daidzein, Genistein, Glycitein | Soybeans, soy foods, legumes |

**Figure 2. Chemical Structures of Some Anthocyanidins (Anthocyanin Aglycones)**

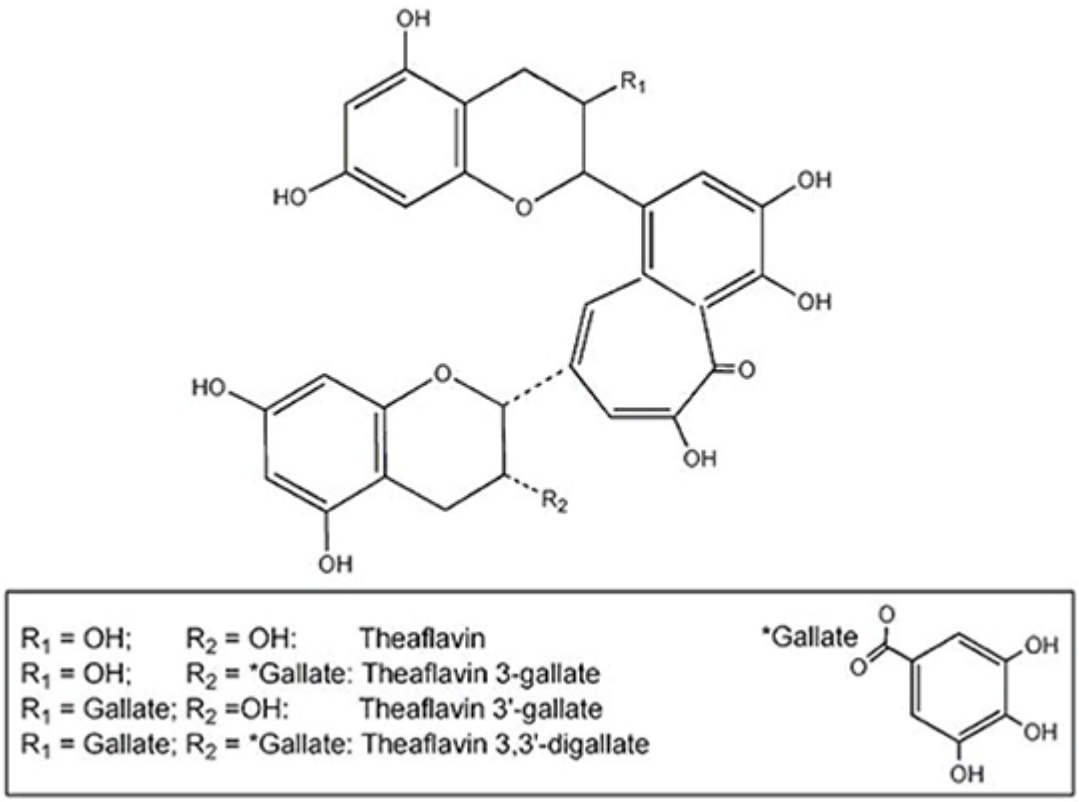



| | | |
|---|---|---|
| $R_1$ = H; | $R_2$ = H: | Pelagonidin |
| $R_1$ = OH; | $R_2$ = H: | Cyanidin |
| $R_1$ = OH; | $R_2$ = OH: | Delphinidin |
| $R_1$ = $OCH_3$; | $R_2$ = OH: | Petunidin |
| $R_1$ = $OCH_3$; | $R_2$ = $OCH_3$: | Malvidin |

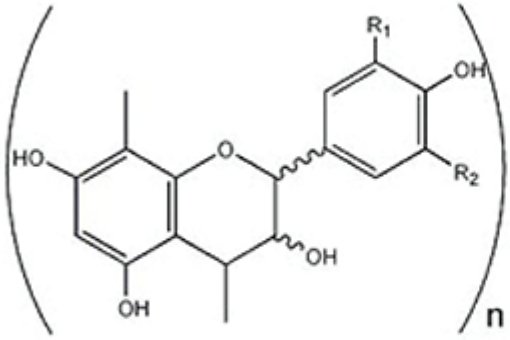
## Figure 3. Chemical Structures of Some Flavanol Monomers (Catechins)



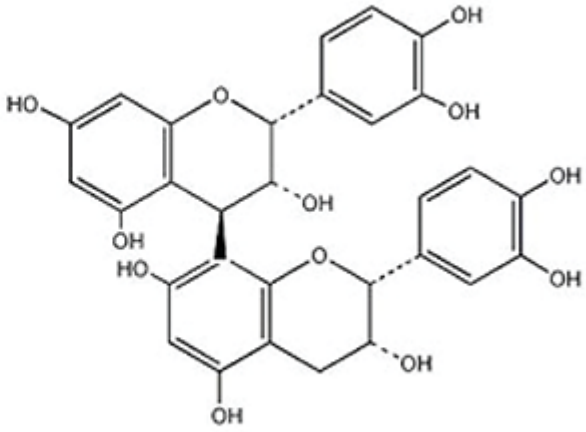

## Figure 4. Chemical Structures of Theaflavins (Flavanol Dimers)



## Figure 5. Chemical Structures of Proanthocyanidins (Flavanol Dimers and Polymers)

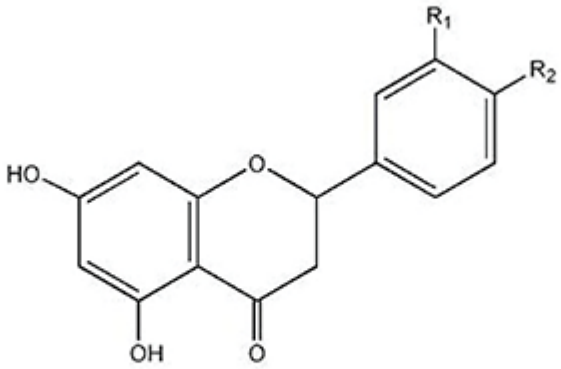



$R_1$ = H; $R_2$ = OH: Procyanidins
$R_1$ = OH; $R_2$ = OH: Prodelphinidins
$R_1$ = H; $R_2$ = H: Propelargonidins



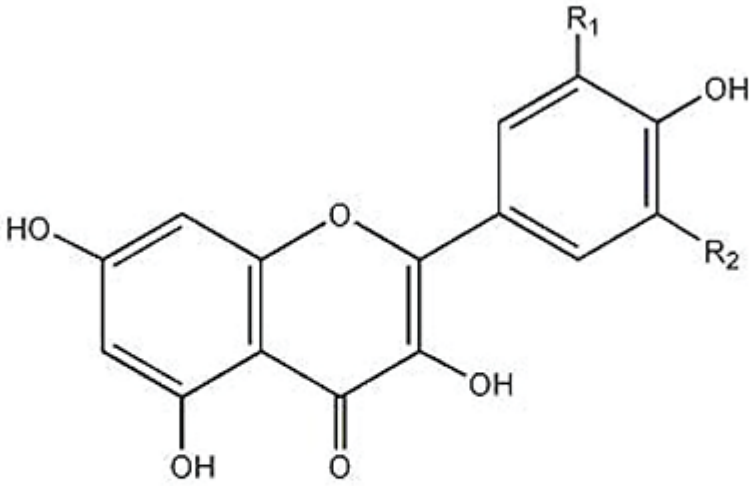

Procyanidin Dimer

## Figure 6. Chemical Structures of Some Flavanones



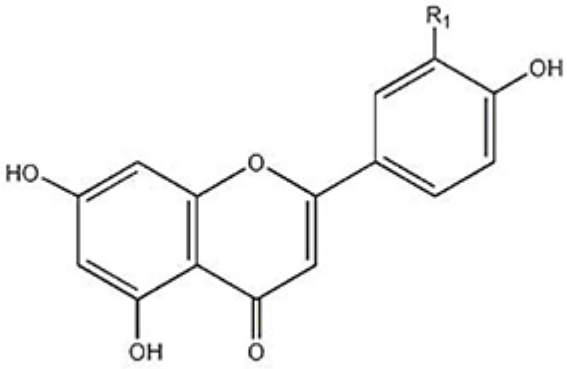

| | | |
|---|---|---|
| $R_1$ = H; | $R_2$ = OH; | Naringenin |
| $R_1$ = OH; | $R_2$ = OH; | Eriodictyol |
| $R_1$ = OH; | $R_2$ = $OCH_3$: | Hesperetin |

## Figure 7. Chemical Structures of Some Flavonols



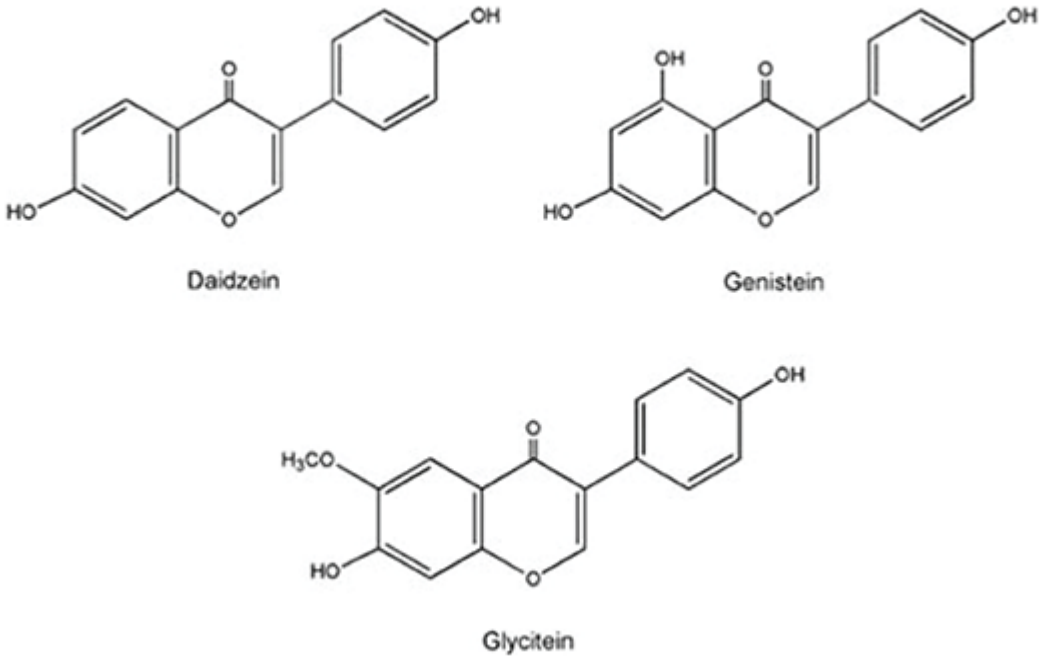

| | | |
|---|---|---|
| $R_1$ = H; | $R_2$ = H: | Kaempferol |
| $R_1$ = OH; | $R_2$ = H: | Quercetin |
| $R_1$ = OH; | $R_2$ OH: | Myricetin |
| $R_1$ = $OCH_3$; | $R_2$ = H: | Isorhamnetin |

## Figure 8. Chemical Structures of Some Flavones




| | |
|---|---|
| $R_1$ = H: | Apigenin |
| $R_1$ = OH: | Luteolin |

**Figure 9. Chemical Structures of Some Isoflavones**




## Metabolism and Bioavailability

Flavonoids connected to one or more sugar molecules are known as flavonoid glycosides, while those that are not connected to a sugar molecule are called aglycones. With the exception of flavanols (catechins and proanthocyanidins), flavonoids occur in plants and most foods as glycosides (2). Even after cooking, most flavonoid glycosides reach the small intestine intact. Only flavonoid aglycones and flavonoid glucosides (bound to glucose) are absorbed in the small intestine, where they are rapidly metabolized to form methylated, glucuronidated, or sulfated metabolites (3). Bacteria that normally colonize the colon also play an important role in flavonoid metabolism and absorption. Flavonoids or flavonoids metabolites that reach the colon may be further metabolized by bacterial enzymes, and then absorbed. A person's ability to produce specific flavonoid metabolites may vary and depends on the milieu of the colonic microflora (4, 5). In general, the bioavailability of flavonoids is relatively low due to limited absorption and rapid elimination. Bioavailability differs for the various flavonoids: isoflavones are the most bioavailable group of flavonoids, while flavanols (proanthocyanidins and tea catechins) and anthocyanins are very poorly absorbed (6). Since flavonoids are rapidly and extensively metabolized, the biological activities of flavonoid metabolites are not always the same as those of the parent compound (reviewed in 7) When evaluating the data from flavonoid research in cultured cells, it is important to consider whether the flavonoid concentrations and metabolites used are physiologically relevant (8). In humans, peak plasma concentrations of soy isoflavones and citrus flavanones have not been found to exceed 10 micromoles/liter after oral consumption. Peak plasma concentrations measured after the consumption of anthocyanins, flavanols and flavonols (including those from tea) are generally less than 1 micromole/liter (3).

## Biological Activities

### Direct antioxidant activity

Flavonoids are effective scavengers of free radicals in the test tube (*in vitro*) (9, 10). However, even with very high flavonoid intakes, plasma and intracellular flavonoid concentrations in humans are likely to be 100-1,000 times lower than concentrations of other antioxidants, such as ascorbate (vitamin C), uric acid, or glutathione. Moreover, most circulating flavonoids are actually flavonoid metabolites, some of which have lower antioxidant activity than the parent flavonoid. For these reasons, the relative contribution of dietary flavonoids to plasma and tissue antioxidant function *in vivo* is likely to be very small or negligible (7, 11, 12).

## Metal chelation

Metal ions, such as iron and copper, can catalyze the production of free radicals. The ability of flavonoids to chelate (bind) metal ions appears to contribute to their antioxidant activity *in vitro* (13, 14). In living organisms, most iron and copper are bound to proteins, limiting their participation in reactions that produce free radicals. Although the metal-chelating activities of flavonoids may be beneficial in pathological conditions of iron or copper excess, it is not known whether flavonoids or their metabolites function as effective metal chelators *in vivo* (11).

## Effects on cell-signaling pathways

Cells are capable of responding to a variety of different stresses or signals by increasing or decreasing the availability of specific proteins. The complex cascades of events that lead to changes in the expression of specific genes are known as cell-signaling pathways or signal transduction pathways. These pathways regulate numerous cell processes, including growth, proliferation, and death (apoptosis). Although it was initially hypothesized that the biological effects of flavonoids would be related to their antioxidant activity, available evidence from cell culture experiments suggests that many of the biological effects of flavonoids are related to their ability to modulate cell-signaling pathways (7). Intracellular concentrations of flavonoids required to affect cell-signaling pathways are considerably lower than those required to affect cellular antioxidant capacity. Flavonoid metabolites may retain their ability to interact with cell-signaling proteins even if their antioxidant activity is diminished (15, 16). Effective signal transduction requires proteins known as kinases that catalyze the phosphorylation of target proteins at specific sites. Cascades involving specific phosphorylations or dephosphorylations of signal transduction proteins ultimately affect the activity of transcription factors — proteins that bind to specific response elements on DNA and promote or inhibit the transcription of various genes. The results of numerous studies in cell culture suggest that flavonoids may affect chronic disease by selectively inhibiting kinases (7, 17). Cell growth and proliferation are also regulated by growth factors that initiate cell-signaling cascades by binding to specific receptors in cell membranes. Flavonoids may alter growth factor signaling by inhibiting receptor phosphorylation or blocking receptor binding by growth factors (18).

Modulation of cell-signaling pathways by flavonoids could help prevent cancer by:

**Stimulating phase II detoxification enzyme activity** (19, 20): Phase II detoxification enzymes catalyze reactions that promote the excretion of potentially toxic or carcinogenic chemicals.

**Preserving normal cell cycle regulation** (21, 22): Once a cell divides, it passes through a sequence of stages collectively known as the cell cycle before it divides again. Following DNA damage, the cell cycle can be transiently arrested at damage checkpoints, which allows for DNA repair or activation of pathways leading to cell death (apoptosis) if the damage is irreparable (23). Defective cell cycle regulation may result in the propagation of mutations that contribute to the development of cancer.

**Inhibiting proliferation and inducing apoptosis** (24-26): Unlike normal cells, cancer cells proliferate rapidly and lose the ability to respond to cell death signals that initiate apoptosis.

**Inhibiting tumor invasion and angiogenesis** (27, 28): Cancerous cells invade normal tissue aided by enzymes called matrix-metalloproteinases. To fuel their rapid growth, invasive tumors must develop new blood vessels by a process known as angiogenesis.

**Decreasing inflammation** (29-31): Inflammation can result in locally increased production of free radicals by inflammatory enzymes, as well as the release of inflammatory mediators that promote cell proliferation and angiogenesis and inhibit apoptosis (32).

Modulation of cell-signaling pathways by flavonoids could help prevent cardiovascular disease by:

**Decreasing inflammation** (29-31): Atherosclerosis is now recognized as an inflammatory

disease, and several measures of inflammation are associated with increased risk of myocardial infarction (heart attack) (33).

**Decreasing vascular cell adhesion molecule expression** (34, 35): One of the earliest events in the development of atherosclerosis is the recruitment of inflammatory white blood cells from the blood to the arterial wall. This event is dependent on the expression of adhesion molecules by the vascular endothelial cells that line the inner walls of blood vessels (36).

**Increasing endothelial nitric oxide synthase (eNOS) activity** (37): eNOS is the enzyme that catalyzes the formation of nitric oxide by vascular endothelial cells. Nitric oxide is needed to maintain arterial relaxation (vasodilation). Impaired nitric oxide-dependent vasodilation is associated with increased risk of cardiovascular disease (38).

**Decreasing platelet aggregation** (39, 40): Platelet aggregation is one of the first steps in the formation of a blood clot that can occlude a coronary or cerebral artery, resulting in myocardial infarction or stroke, respectively. Inhibiting platelet aggregation is considered an important strategy in the primary and secondary prevention of cardiovascular disease (41).

## Disease Prevention

## Cardiovascular disease

### *Epidemiological evidence*

Several prospective cohort studies conducted in the US and Europe have examined the relationship between some measure of dietary flavonoid intake and coronary heart disease (CHD) risk (42-49). Some studies have found that higher flavonoid intakes to be associated with significant reductions in CHD risk (42-46, 50), while others have reported no significant relationship (47-49, 51). In general, the foods that contributed most to total flavonoid intake in these cohorts were black tea, apples, and onions. One study in the Netherlands also found cocoa to be a significant source of dietary flavonoids. Of seven prospective cohort studies that examined relationships between dietary flavonoid intake and the risk of stroke, only two studies found that higher flavonoid intakes were associated with significant reductions in the risk of stroke (45, 52), while five found no relationship (46, 49, 50, 53, 54). Although data from prospective cohort studies suggest that higher intakes of flavonoid-rich foods may help protect against CHD, it cannot be determined whether such protection is conferred by flavonoids, other nutrients and phytochemicals in flavonoid-rich foods, or the whole foods themselves (55).

### *Vascular endothelial function*

Vascular endothelial cells play an important role in maintaining cardiovascular health by producing nitric oxide, a compound that promotes arterial relaxation (vasodilation) (56). Arterial vasodilation resulting from endothelial production of nitric oxide is termed endothelium-dependent vasodilation. Several clinical trials have examined the effect of flavonoid-rich foods and beverages on endothelium-dependent vasodilation. Two controlled clinical trials found that daily consumption of 4-5 cups (900-1,250 mL) of black tea for four weeks significantly improved endothelium-dependent vasodilation in patients with coronary artery disease (57) and in patients with mildly elevated serum cholesterol levels (58) compared with the equivalent amount of caffeine alone or hot water. Other small clinical trials found similar improvements in endothelium-dependent vasodilation in response to daily consumption of about 3 cups (640 mL) of purple grape juice (59) or a high-flavonoid dark chocolate bar for two weeks (60). More recently, a six-week cocoa intervention trial in 32 postmenopausal women with high cholesterol levels found significant improvements in endothelial function with daily cocoa supplementation (61). Improvements in endothelial function were also noted in conventionally medicated type 2 diabetics following flavanol-rich cocoa supplementation for 30 days (62). The flavanol epicatechin appears to be one of the compounds in flavanol-rich cocoa responsible for its vasodilatory effects (63). Interestingly, a recent randomized controlled trial in 44 older adults found that low doses of flavonoid-rich dark chocolate (6.3 grams/day for 18 weeks; equivalent to 30 calories) increased levels of plasma S-

nitrosoglutathione, an indicator of nitric oxide production, compared to flavonoid-devoid white chocolate (64).

Endothelial nitric oxide production also inhibits the adhesion and aggregation of platelets, one of the first steps in blood clot formation (56). A number of clinical trials have examined the potential for high flavonoid intakes to decrease various measures of platelet aggregation outside of the body ( *ex vivo*); such trials have reported mixed results. In general, increasing flavonoid intakes by increasing fruit and/or vegetable intake did not significantly affect *ex vivo* platelet aggregation (41, 65, 66), nor did increasing black tea consumption (67, 68). However, several small clinical trials in healthy adults have reported significant decreases in *ex vivo* measures of platelet aggregation after consumption of grape juice (~500 mL/day) for 7-14 days (69-71). Similar inhibition of platelet aggregation has been reported following acute or short-term consumption of dark chocolate (72) and following acute consumption of a flavonoid-rich cocoa beverage (73, 74). In addition, a placebo-controlled trial in 32 healthy adults found that four-week supplementation with flavanols and procyanidins from cocoa inhibited platelet aggregation and function (75). The results of some controlled clinical trials suggest that relatively high intakes of some flavonoid-rich foods and beverages, including black tea, purple grape juice, and cocoa, may improve vascular endothelial function, but it is not known whether these short-term improvements will result in long-term reductions in cardiovascular disease risk.

## Cancer

Although various flavonoids have been found to inhibit the development of chemically-induced cancers in animal models of lung (76), oral (77), esophageal (78), stomach (79), colon (80), skin (81), prostate (82, 83), and mammary (breast) cancer (84), epidemiological studies do not provide convincing evidence that high intakes of dietary flavonoids are associated with substantial reductions in human cancer risk. Most prospective cohort studies that have assessed dietary flavonoid intake using food frequency questionnaires have not found flavonoid intake to be inversely associated with cancer risk (85). Two prospective cohort studies in Europe found no relationship between the risk of various cancers and dietary intakes of flavones and flavonols (86, 87), catechins (88), or tea (89). In a cohort of postmenopausal women in the US, catechin intake from tea, but not fruit and vegetables, was inversely associated with the risk of rectal cancer, but not other cancers (90). Two prospective cohort studies in Finland, where average flavonoid intakes are relatively low, found that men with the highest dietary intakes of flavonols and flavones had a significantly lower risk of developing lung cancer than those with the lowest intakes (44, 45). When individual dietary flavonoids were analyzed, dietary quercetin intake, mainly from apples, was inversely associated with the risk of lung cancer; myricetin intake was inversely associated with the risk of prostate cancer (45). Tea is an important source of flavonoids (flavanols and flavonols) in some populations, but most prospective cohort studies have not found tea consumption to be inversely associated with cancer risk (reviewed in 91). The results of case-control studies, which are more likely to be influenced by recall bias, are mixed. While some studies have observed lower flavonoid intakes in people diagnosed with lung (92), stomach (93, 94), and breast (95) cancer, many others have found no significant differences in flavonoid intake between cancer cases and controls (96, 97). There is limited evidence that low intakes of flavonoids from food are associated with increased risk of certain cancers, but it is not clear whether these findings are related to insufficient intakes of flavonoids or other nutrients and phytochemicals found in flavonoid-rich foods. For more information on flavonoid-rich foods and cancer, see separate articles on Fruit and Vegetables, Legumes, and Tea. Clinical trials will be necessary to determine if specific flavonoids are beneficial in the prevention or treatment of cancer; a few clinical trials are currently under way (see http://www.cancer.gov/about-cancer/treatment/clinical-trials).

## Neurodegenerative diseases

Inflammation, oxidative stress, and transition metal accumulation appear to play a role in the pathology of several neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease (98). Because flavonoids have anti-inflammatory, antioxidant, and metal-chelating properties, scientists are interested in the neuroprotective potential of flavonoid-rich diets or individual flavonoids. At present, the extent to which various dietary flavonoids and flavonoid metabolites cross the blood brain barrier in humans is not known (99, 100). Although flavonoid-

rich diets and flavonoid administration have been found to prevent cognitive impairment associated with aging and inflammation in some animal studies (101-104), prospective cohort studies have not found consistent inverse associations between flavonoid intake and the risk of dementia or neurodegenerative disease in humans (105-109). In a cohort of Japanese-American men followed for 25-30 years, flavonoid intake from tea during midlife was not associated with the risk of Alzheimer's or other types of dementia in late life (105). Surprisingly, higher intakes of isoflavone-rich tofu during midlife were associated with cognitive impairment and brain atrophy in late life (see the article on Soy Isoflavones) (106). A prospective study of Dutch adults found that total dietary flavonoid intake was not associated with the risk of developing Parkinson's disease (107) or Alzheimer's disease (108), except in current smokers whose risk of Alzheimer's disease decreased by 50% for every 12 mg increase in daily flavonoid intake. In contrast, a study of elderly French men and women found that those with the lowest flavonoid intakes had a risk of developing dementia over the next five years that was 50% higher than those with the highest intakes (109). More recently, a study in 1,640 elderly men and women found that those with higher dietary flavonoid intake (>13.6 mg/day) had better cognitive performance at baseline and experienced significantly less age-related cognitive decline over a 10-year period than those with a lower flavonoid intake (0-10.4 mg/day) (110). Additionally, a randomized, double-blind, placebo-controlled clinical trial in 202 postmenopausal women reported that daily supplementation with 25.6 g of soy protein (containing 99 mg of isoflavones) for one year did not improve cognitive function (111). However, a randomized, double-blind, placebo-controlled, cross-over trial in 77 postmenopausal women found that six-month supplementation with 60 mg/day of isoflavones improved some measures of cognitive performance (112). Although scientists are interested in the potential of flavonoids to protect the aging brain, it is not yet clear how flavonoid consumption affects neurodegenerative disease risk in humans.

## Sources

## Food sources

Dietary sources of flavonoids include tea, red wine, fruit, vegetables, and legumes. Individual flavonoid intakes may vary considerably depending on whether tea, red wine, soy products, or fruit and vegetables are commonly consumed (reviewed in 3). Although individual flavonoid intakes may vary, total flavonoid intakes in Western populations appear to average about 150-200 mg/day (3, 113). Information on the flavonoid content of some flavonoid-rich foods is presented in **Table 2** and **Table 3**. These values should be considered approximate since a number of factors may affect the flavonoid content of foods, including agricultural practices, environmental factors, ripening, processing, storing, and cooking. For more information about the flavonoid content of foods, see the USDA databases for the flavonoid and proanthocyanidin content of selected foods. For information on the isoflavone content of soy foods, see the separate article on Soy Isoflavones or the USDA database for the isoflavone content of selected foods.

**Table 2. Anthocyanin, Flavanol, and Proanthocyanidin Content of Selected Foods (mg/100 g or 100 mL*) (3, 129-135)**

| Anthocyanin-rich Foods | Anthocyanins | Flavanols | Proanthocyanidins |
|---|---|---|---|
| Blackberry | 89-211 | 13-19 | 6-47 |
| Blueberry | 67-183 | 1 | 88-261 |
| Grapes, red | 25-92 | 2 | 44-76 |
| Raspberries (red) | 10-84 | 9 | 5-59 |
| Strawberry | 15-75 | - | 97-183 |
| Red wine | 1-35 | 1-55 | 24-70 |
| Plum | 2-25 | 1-6 | 106-334 |

| | | | |
|---|---|---|---|
| Red cabbage | 25 | 0 | - |
| Red onion | 13- 25 | - | - |
| Blood orange juice | 3-10 | - | - |
| **Flavanol-rich Foods** | **Anthocyanins** | **Flavanols** | **Proanthocyanidins** |
| Green tea | - | 24-216 | - |
| Black tea | - | 5-158 | 4 |
| Chocolate, dark | - | 43-63 | 90-322 |
| Apple, red delicious with peel | 1-4 | 2-12 | 89-148 |
| Apricot | - | 10-25 | 8-13 |
| **Flavone-rich Foods** | **Anthocyanins** | **Flavanols** | **Proanthocyanidins** |
| Parsley, fresh | - | - | - |
| Thyme, fresh | - | - | - |
| Celery hearts, green | - | - | - |
| Celery | - | - | - |
| Oregano, fresh | - | - | - |
| Chili peppers, green | - | - | - |
| **Flavanone-rich Foods** | **Anthocyanins** | **Flavanols** | **Proanthocyanidins** |
| Lemon juice, fresh | - | - | - |
| Grapefruit juice, fresh | - | - | - |
| Orange juice, fresh | - | - | - |
| Grapefruit, fresh | - | - | - |
| Orange, fresh | - | - | - |
| **Flavonol-rich Foods** | **Anthocyanins** | **Flavanols** | **Proanthocyanidins** |
| Onion, yellow | - | 0 | - |
| Kale | - | - | - |
| Leek | - | 0 | - |
| Broccoli | - | 0 | - |

*per 100 g (fresh weight) or 100 mL (liquids); 100 grams is equivalent to about 3.5 ounces; 100 mL is equivalent to about 3.5 fluid ounces.

**Table 3. Flavone, Flavonol, and Flavanone Content of Selected Foods (mg/100 g or 100 mL*) (3, 129-135)**

| **Anthocyanin-rich Foods** | **Flavones** | **Flavonols** | **Flavanones** |
|---|---|---|---|
| Blackberry | - | 0-2 | - |
| Blueberry | - | 2-16 | - |
| Grapes, red | - | 3-4 | - |

| | | | |
|---|---|---|---|
| Raspberries (red) | - | 1 | - |
| Strawberry | - | 1-4 | - |
| Red wine | 0 | 2-30 | - |
| Plum | 0 | 1-2 | - |
| Red cabbage | 0-1 | 0-1 | - |
| Red onion | 0 | 4-100 | - |
| Blood orange juice | - | - | 10-22 |
| **Flavanol-rich Foods** | **Flavones** | **Flavonols** | **Flavanones** |
| Green tea | 0-1 | 3-9 | - |
| Black tea | 0 | 1-7 | - |
| Chocolate, dark | - | - | - |
| Apple, red delicious with peel | 0 | 2-6 | - |
| Apricot | 0 | 2-5 | - |
| **Flavone-rich Foods** | **Flavones** | **Flavonols** | **Flavanones** |
| Parsley, fresh | 24-634 | 8-10 | - |
| Thyme, fresh | 56 | 0 | - |
| Celery hearts, green | 23 | - | - |
| Celery | 0-15 | 4 | - |
| Oregano, fresh | 2-7 | 0 | - |
| Chili peppers, green | 5 | 13-21 | - |
| **Flavanone-rich Foods** | **Flavones** | **Flavonols** | **Flavanones** |
| Lemon juice, fresh | 0 | 0-2 | 2-175 |
| Grapefruit juice, fresh | 0 | 0 | 10-104 |
| Orange juice, fresh | 0-1 | 0 | 5-47 |
| Grapefruit, fresh | - | 1 | 55 |
| Orange, fresh | - | - | 42-53 |
| **Flavonol-rich Foods** | **Flavones** | **Flavonols** | **Flavanones** |
| Onion, yellow | 0 | 3-120 | - |
| Kale | 0 | 30-60 | - |
| Leek | 0 | 3-22 | - |
| Broccoli | 0 | 4-13 | - |

*per 100 g (fresh weight) or 100 mL (liquids); 100 grams is equivalent to about 3.5 ounces; 100 mL is equivalent to about 3.5 fluid ounces.

## Supplements

*Anthocyanins*

Bilberry, elderberry, black currant, blueberry, red grape, and mixed berry extracts that are rich in

anthocyanins are available as dietary supplements without a prescription in the US. The anthocyanin content of these products may vary considerably. Standardized extracts that list the amount of anthocyanins per dose are available.

*Flavanols*

Numerous tea extracts are available in the US as dietary supplements and may be labeled as tea catechins or tea polyphenols. Green tea extracts are the most commonly marketed, but black and oolong tea extracts are also available. Green tea extracts generally have higher levels of catechins (flavanol monomers), while black tea extracts are richer in theaflavins and thearubigins (flavanol polymers found in tea). Oolong tea extracts fall somewhere in between green and black tea extracts with respect to their flavanol content. Some tea extracts contain caffeine, while others are decaffeinated. Flavanol and caffeine content vary considerably among different products, so it is important to check the label or consult the manufacturer to determine the amounts of flavanols and caffeine that would be consumed daily with each supplement. For more information on tea flavanols, see the article on Tea.

*Flavanones*

Citrus bioflavonoid supplements may contain glycosides of hesperetin (hesperidin), naringenin (naringin), and eriodictyol (eriocitrin). Hesperidin is also available in hesperidin-complex supplements (114).

*Flavones*

The peels of citrus fruit are rich in polymethoxylated flavones: tangeretin, nobiletin, and sinensetin (3). Although dietary intakes of these naturally occurring flavones are generally low, they are often present in citrus bioflavonoid supplements.

*Flavonols*

The flavonol aglycone, quercetin, and its glycoside rutin are available as dietary supplements without a prescription in the US. Other names for rutin include rutinoside, quercetin-3-rutinoside, and sophorin (114). Citrus bioflavonoid supplements may also contain quercetin or rutin.

## Safety

## Adverse effects

No adverse effects have been associated with high dietary intakes of flavonoids from plant-based foods. This lack of adverse effects may be explained by the relatively low bioavailability and rapid metabolism and elimination of most flavonoids.

*Quercetin*

Some men taking quercetin supplements (1,000 mg/day for one month) reported nausea, headache, or tingling of the extremities (115). Some cancer patients given intravenous quercetin in a phase I clinical trial reported nausea, vomiting, sweating, flushing, and dyspnea (difficulty breathing) (116). Intravenous administration of quercetin at doses of 945 mg/m$^2$ or more was associated with renal (kidney) toxicity in that trial.

*Tea extracts*

There have been several reports of hepatotoxicity (liver toxicity) following consumption of supplements containing tea (Camellia sinensis) extracts (117, 118). In clinical trials of caffeinated

green tea extracts, cancer patients who took 6 g/day in 3-6 divided doses have reported mild to moderate gastrointestinal side effects, including nausea, vomiting, abdominal pain, and diarrhea (119, 120). Central nervous system symptoms, including agitation, restlessness, insomnia, tremors, dizziness, and confusion, have also been reported. In one case, confusion was severe enough to require hospitalization (119). These side effects were likely related to the caffeine in the green tea extract (120). In a four-week clinical trial that assessed the safety of decaffeinated green tea extracts (800 mg/day of EGCG) in healthy individuals, a few of the participants reported mild nausea, stomach upset, dizziness, or muscle pain (121).

## Pregnancy and lactation

The safety of flavonoid supplements in pregnancy and lactation has not been established (114).

## Drug interactions

### *Inhibition of CYP 3A4 by grapefruit juice and flavonoids*

As little as 200 mL (7 fluid ounces) of grapefruit juice has been found to irreversibly inhibit the intestinal drug metabolizing enzyme, cytochrome P450 (CYP) 3A4 (122). Although the most potent inhibitors of CYP3A4 in grapefruit are thought to be furanocoumarins, particularly dihydroxybergamottin, the flavonoids naringenin and quercetin have also been found to inhibit CYP3A4 *in vitro*. Inhibition of intestinal CYP3A4 can increase the bioavailability and the risk of toxicity of a number of drugs, including but not limited to HMG-CoA reductase inhibitors (atorvastatin, lovastatin, and simvastatin), calcium channel antagonists (felodipine, nicardipine, nisoldipine, nitrendipine, and verapamil), anti-arrhythmic agents (amiodarone), HIV protease inhibitors (saquinavir), immunosuppressants (cyclosporine), antihistamines (terfenadine), gastrointestinal stimulants (cisapride), benzodiazepines (diazepam, midazolam, and triazolam), anticonvulsants (carbamazepine), anxiolytics (buspirone) serotonin specific reuptake inhibitors (sertraline), and drugs used to treat erectile dysfunction (sildenafil) (123). Grapefruit juice may reduce the therapeutic effect of the angiotensin II receptor antagonist, losartan. Because of the potential for adverse drug interactions, some clinicians recommend that people taking medications that undergo extensive presystemic metabolism by CYP3A4 avoid consuming grapefruit juice altogether to avoid potential toxicities (122).

### *Inhibition of P-glycoprotein by grapefruit juice and flavonoids*

P-glycoprotein is an efflux transporter that decreases the absorption of a number of drugs. There is some evidence that the consumption of grapefruit juice inhibits the activity of P-glycoprotein (122). Quercetin, naringenin, and the green tea flavanol, epigallocatechin gallate (EGCG), have been found to inhibit the efflux activity of P-glycoprotein in cultured cells (124). Thus, very high or supplemental intakes of these flavonoids could potentially increase flavonoid bioavailability, potentially increasing the toxicity of drugs that are substrates of P-glycoprotein. Drugs known to be substrates of P-glycoprotein include digoxin, antihypertensive agents, antiarrhythmic agents, chemotherapeutic (anticancer) agents, antifungal agents, HIV protease inhibitors, immunosuppressive agents, H2 receptor antagonists, some antibiotics, and others (reviewed in 125).

### *Anticoagulant and antiplatelet drugs*

High intakes of flavonoids from purple grape juice (500 mL/day) and dark chocolate (235 mg/day of flavanols) have been found to inhibit platelet aggregation in *ex vivo* assays (69-71, 75). Theoretically, high intakes of flavonoids (e.g., from supplements) could increase the risk of bleeding when taken with anticoagulant drugs, such as warfarin (Coumadin), and antiplatelet drugs, such as clopidogrel (Plavix), dipyridamole (Persantine), non-steroidal anti-inflamatory drugs (NSAIDs), aspirin, and others.

## Nutrient interactions

*Nonheme iron*

Flavonoids can bind nonheme iron, inhibiting its intestinal absorption. Nonheme iron is the principal form of iron in plant foods, dairy products, and iron supplements. The consumption of one cup of tea or cocoa with a meal has been found to decrease the absorption of nonheme iron in that meal by about 70% (126, 127). To maximize iron absorption from a meal or iron supplements, flavonoid-rich beverages or flavonoid supplements should not be taken at the same time.

*Vitamin C*

Studies in cell culture indicate that a number of flavonoids inhibit the transport of vitamin C into cells, and supplementation of rats with quercetin and vitamin C decreased the intestinal absorption of vitamin C (128). More research is needed to determine the significance of these findings in humans.

## Authors and Reviewers

Originally written in 2005 by:
Jane Higdon, Ph.D.
Linus Pauling Institute
Oregon State University

Updated in June 2008 by:
Victoria J. Drake, Ph.D.
Linus Pauling Institute
Oregon State University

Reviewed in June 2008 by:
Roderick H. Dashwood, Ph.D.
Director, Cancer Chemoprotection Program, Linus Pauling Institute
Professor of Environmental & Molecular Toxicology
Leader, Environmental Mutagenesis & Carcinogenesis Core, Environmental Health Sciences Center

Oregon State University



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307 Linus Pauling Science Center | Corvallis, Oregon 97331
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