

Flavonoids¹

With >4000 compounds, flavonoids are the most abundant polyphenols present in plant foods (1). They are characterized by a 15-carbon skeleton, organized as C₆-C₃-C₆, with different substitutions making up the different subclasses (Fig. 1). The major groups of flavonoids of nutritional interest are the flavanols, or catechins (e.g., epigallocatechin 3-gallate from green tea), the flavones (e.g., apigenin from celery), the flavonols (e.g., quercetin, ubiquitous in plant foods, particularly red onion and apple), the flavanones (e.g., naringenin from citrus), the anthocyanidins (e.g., cyanidin from berries), and the isoflavones (e.g., genistein and daidzein from soya beans). Whereas flavones and flavonols can be found naturally as the aglycone, flavonoids typically are stored in the plant bound to sugar(s), termed glycosides, which are more stable than the free flavonoids but have relatively poor bioavailability when ingested (1), often requiring hydrolysis to the aglycone. Breakdown of oligomers may occur in the stomach acid, although hydrolysis of monomers and absorption of their aglycones appear to occur to a greater degree in the small intestine, involving epithelial enzymes within the brush border and the cytosol of the enterocytes (2). Once absorbed, flavonoids are mostly found as conjugates, with recent studies suggesting that tissue β-glucuronidase may release active aglycones from stable circulating glucuronides (1).

Flavonoids are bioactive dietary constituents that may enhance health and help prevent chronic disease. The strongest evidence for chronic disease prevention is in the area of vascular health (3), where a meta-analysis revealed improvements in flow-mediated dilatation and blood pressure. Fewer studies have assessed the potential role of flavonoid intake in the protection against diabetes, but a recent review of clinical trials confirmed that foods containing both anthocyanidins (berries) and flavan 3-ols (green tea and cocoa) provide some protection against type II diabetes and cardiovascular disease (3). Although possibly only partly responsible, one mechanism for protection against diabetes appears to be that flavonoids disrupt the glucose uptake systems SGLT1 and GLUT2 (4). Another mechanism of antidiabetes may be inhibition of α-glucosidase (4). Many retrospective and prospective studies have assessed the potential role of flavonoids in cancer prevention, and although some observations have been promising, study results have been inconsistent and prospective studies with more subjects are needed (5). Studies are emerging to suggest slowing of neurodegenerative diseases with intake of dietary berries and/or flavonoids (6). Both neural and systemic anti-inflammatory activities of flavonoids have been reported and may be the key underlying action in prevention of many chronic diseases (1). No deficiency disease has been identified for flavonoids.

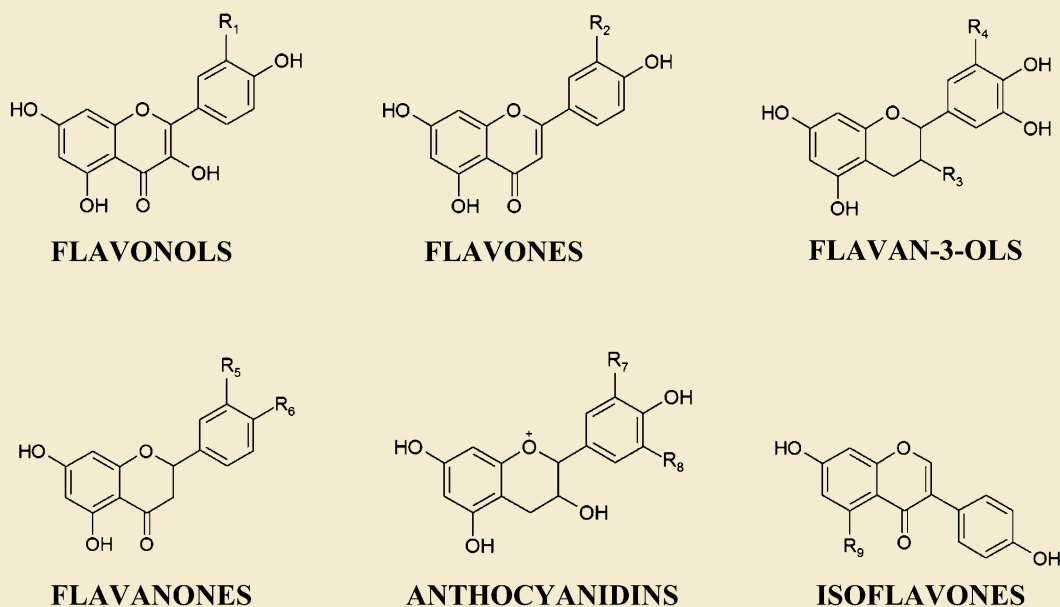


FIGURE 1 Flavonoid structures. R₁ = H: kaempferol; R₁ = OH: quercetin; R₂ = H: apigenin; R₂ = OH: luteolin; R₃ = OH, R₄ = H: catechin; R₃ = gallate, R₄ = OH: gallic acid; R₃ = gallate, R₄ = OH: epigallocatechin-3-gallate; R₅ = H, R₆ = OH: naringenin; R₅ = OH, R₆ = OCH₃: hesperetin; R₇ = OH, R₈ = H: cyanidin, R₇ = OCH₃, R₈ = OCH₃: malvidin; R₉ = H: daidzein; R₉ = OH: genistein.

Diet recommendations: A DRI has not been established for flavonoids. Although flavonoids are not essential nutrients, because they do not appear to be necessary for growth and development, it has been suggested that they are “life span essential,” meaning that their presence in the diet can reduce risk for chronic disease (7).

Food sources: The development of the USDA database of flavonoid content of selected foods has allowed sources and intakes to be estimated (8), and major dietary food sources include beverages (green tea, cocoa, coffee, red wine), fruits (berries, apple, citrus), and vegetables (cruciferous and colorful vegetables). Flavonoid intake in human diets is estimated to be 20–200 mg/d, although tea drinkers may reach ≥ 1000 mg/d (1).

Clinical uses: An important clinical implication of flavonoids is the potential interaction with many standard drug therapies as exemplified by grapefruit-drug interactions, which are believed to be due to flavonoid interference with P-glycoprotein and drug uptake transporters such as organic anion-transporting polypeptides (9). Moreover, flavonoids have shown potential for use as cyclin-dependent kinase inhibitor drugs, with the synthetic flavopiridol reaching the clinic (10).

Toxicity: A tolerable upper DRI has not been established for flavonoids, and when they are consumed at amounts found in foods, toxicity is not a concern (1). However, the potential for flavonoid toxicity exists if they are consumed at extraordinary amounts in the form of high-potency supplements. In addition, flavonoids are potentially toxic in vulnerable populations such as the elderly who are marginally iron deficient, because flavonoids may bind nonheme iron (1).

Recent research: In addition to extensive investigations into health impacts of flavonoids, their mechanisms of action have garnered considerable interest. Because flavonoids are polyphenolic and are able to quench free radicals, they have commonly been termed antioxidants. Whereas this property may prove to be useful in studies of food shelf life, it is extremely unlikely that the health benefits of ingesting flavonoids are associated with direct-acting antioxidant action (1). Flavonoids are not recycled in the body in the manner of vitamins E and C, and systemically, they are considerably lower in concentration than these “antioxidant vitamins” and are more likely to have

biological effects by binding lipids and/or proteins (1). For further information, see (11,12).

Diane F. Birt*
Department of Food Science and Human Nutrition, Iowa State University, Ames, IA

Elizabeth Jeffery
Department of Food Science and Human Nutrition, University of Illinois, Urbana-Champaign, Urbana, IL

¹Author disclosures: D. F. Birt and E. Jeffery, no conflicts of interest.

*To whom correspondence should be addressed. E-mail: dbirt@iastate.edu.

Literature Cited

1. Corcoran MP, McKay DL, Blumberg JB. Flavonoid basics: chemistry, sources, mechanisms of action, and safety. *J Nutr Gerontol Geriatr.* 2012;31:176–89.
2. Németh K, Plumb GW, Berrin JG, Juge N, Jacob R, Naim HY, Williamson G, Swallow DM, Kroon PA. Deglycosylation by small intestinal epithelial cell beta-glucosidases is a critical step in the absorption and metabolism of dietary flavonoid glycosides in humans. *Eur J Nutr.* 2003;42:29–42.
3. van Dam RM, Naidoo N, Landberg R. Dietary flavonoids and the development of type 2 diabetes and cardiovascular diseases: review of recent findings. *Curr Opin Lipidol.* 2013;24:25–33.
4. Williamson G. Possible effects of dietary polyphenols on sugar absorption and digestion. *Mol Nutr Food Res.* 2013;57:48–57.
5. Jin H, Leng Q, Li C. Dietary flavonoid for preventing colorectal neoplasms. *Cochrane Database Syst Rev.* 2012;8:CD009350. doi: 10.1002/14651858.CD009350.pub2.
6. Devore EE, Kang JH, Breteler MMB, Grodstein F. Dietary intakes of berries and flavonoids in relation to cognitive decline. *Ann Neurol.* 2012;72:135–43.
7. Williamson G, Holst B. Dietary reference intake (DRI) value for dietary polyphenols: are we heading in the right direction? *Br J Nutr.* 2008;99:S55–8.
8. Bhagwat S, Haytowitz DB, Holden JM. USDA database for the flavonoid content of selected foods. Release 3. Beltsville, MD: USDA; 2011.
9. Seden K, Dickinson L, Khoo S, Back D. Grapefruit-drug interactions. *Drugs.* 2010;70:2373–407.
10. Cragg GM, Newman DJ. Plants as a source of anti-cancer agents. *J Ethnopharmacol.* 2005;100:72–9.
11. Fereidoon S, Nacz M. Phenolics in food and nutraceuticals. Boca Raton, FL: CRC Press; 2006.
12. Anderson OM, Markham KR. Flavonoids: chemistry, biochemistry and applications. Boca Raton, FL: CRC Press; 2006.