REVIEW

Flavones: Food Sources, Bioavailability, Metabolism, and Bioactivity[1,2]

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ABSTRACT

Flavones are a class of flavonoids that are a subject of increasing interest because of their biological activities in vitro and in vivo. This article reviews the major sources of flavones and their concentrations in food and beverages, which vary widely between studies. It also covers the roles of flavones in plants, the influence of growing conditions on their concentrations, and their stability during food processing. The absorption and metabolism of flavones are also reviewed, in particular the intestinal absorption of both *O*- and *C*-glycosides. Pharmacokinetic studies in both animals and humans are described, comparing differences between species and the effects of glycosylation on bioavailability. Biological activity in animal models and human dietary intervention studies is also reviewed. A better understanding of flavone sources and bioavailability is needed to understand mechanisms of action and nutritional intervention. *Adv Nutr* 2017;8:423–35.

Keywords: flavonoids, absorption, metabolism, apigenin, luteolin, diosmetin, pharmacokinetics

Introduction

Flavonoids are widespread throughout the plant kingdom, and several reviews have examined their food sources and the bioavailability, metabolism, and biological activity of these compounds in humans (1–4). Although extensive, these reviews omitted or only briefly mentioned flavones, likely because of the limited information available in comparison with other flavonoids. Since the publication of these reviews, flavones have been the subject of numerous promising in vitro studies, and many publications have further expanded our knowledge of their pharmacokinetics and activity in humans and in animal models.

This review explores the most common flavones in the diet, their biological role in plants, and the most abundant food sources containing them. It will also delve into the bioavailability of flavones from foods and their metabolism in humans. Finally, the biological activity of flavones in human clinical trials will be discussed.

Current Status of Knowledge

Flavone functions and variability with growing conditions

Flavones differ from other flavonoids in that they have a double bond between C2 and C3 in the flavonoid skeleton, there is no substitution at the C3 position (5), and they are oxidized at the C4 position (**Figure 1**). These compounds play a variety of roles in plants. Along with flavonols, they are the primary pigments in white- and cream-colored flowers (6) and act as copigments with anthocyanins in blue flowers (7). Flavones and other flavonoids can also act as UVB protectants in plants, because they absorb in the 280- to 315-nm range (7). Their synthesis can be upregulated by UV light in parsley cells (8), resulting in apigenin and luteolin concentrations in celery leaves >20 times higher than those in stalks (9) and field-grown plants with higher concentrations than greenhouse grown plants (10, 11). Flavones can also act as natural pesticides in plants, providing protection against insects (6) and fungal diseases (12, 13). Plants grown under organic conditions (with presumably more pest pressure), however, have in most cases shown no higher concentrations of flavones than their conventional counterparts (14–17). Flavones also act as signaling molecules for plants, promoting colonization of roots by nitrogen-fixing bacteria (18) and mycorrhizal fungi (19).

Food sources of flavones

Flavones from plants are typically conjugated as 7-*O*-glycosides (Figure 1) (5), and may also have acetyl or malonyl moieties. Flavone *C*-glycosides are most commonly detected as 6-*C*- and 8-*C*-glucosides. Whereas flavone *O*-glycosides can be hydrolyzed with enzymes or acid before analysis, flavone *C*-glycosides are resistant to both processes and must be

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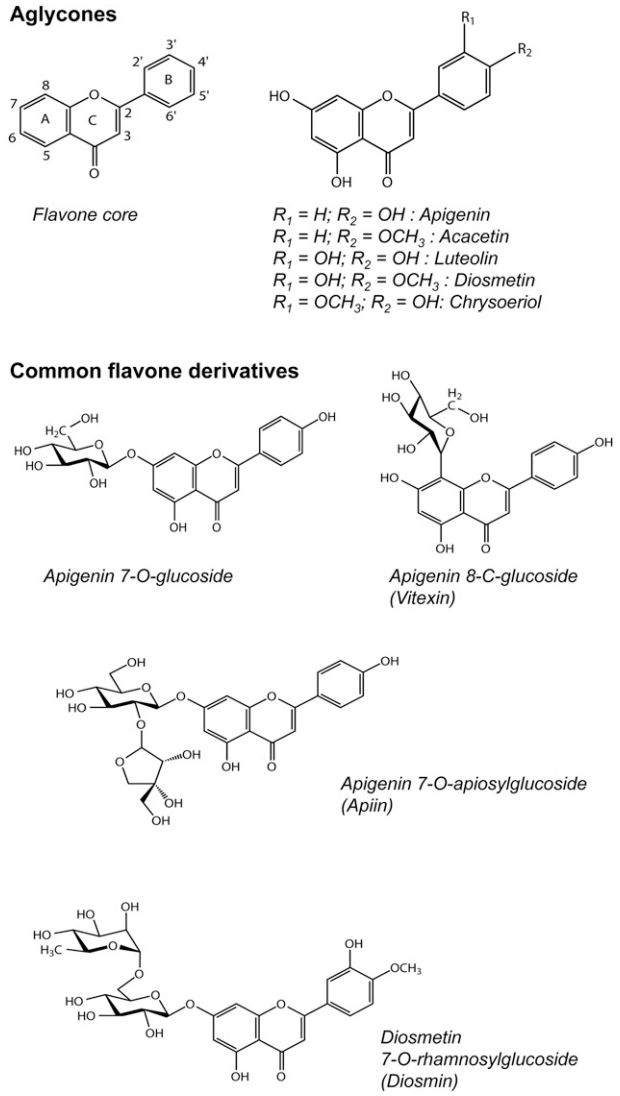

FIGURE 1 Structures of flavone aglycones and common flavone derivatives.

analyzed in their native forms (20). Both glycosides and aglycones are commonly used for quantitation in the literature. Reports on the daily intake of flavones vary, ranging from 0.7 to 9.0 mg/d in adults in Europe (21–23), 1.1 to 1.6 mg/d in women in the United States (24, 25), and 1.9 to 4.2 mg/d in female adolescents in China (26).

Concentrations of flavones in dried tea leaves and herbs are listed in **Table 1**. Chamomile and parsley have the highest flavone concentrations, with as much as 5320 mg apigenin *O*-glycosides/100 g dried chamomile flowers or 1350 mg/100 g dried parsley leaf (28, 29). The apigenin conjugates in chamomile have been identified as acetyl, malonyl, and caffeoyl derivatives of apigenin 7-*O*-glucoside (39), whereas those in parsley are predominantly apigenin 7-*O*-malonyl apiosylglucoside (malonylapiin) and apigenin 7-*O*-apiosylglucoside (apiin) (29). Luteolin 8-*C*-glucoside (orientin) and luteolin 6-*C*-glucoside (isoorientin) are most abundant in rooibos tea (32). Green, black, and oolong teas contain orientin and isoorientin, as well as a variety of apigenin mono- and di-*C*-glycosides (20). Flavone *O*-glycosides are also reported in many plants from the mint family (Lamiaceae), but their reported concentrations vary widely between sources. For example, luteolin glycosides in peppermint ranged from 42 to 3070 mg/100 g dry leaf, varying with the source and the analytic methods used (35, 36).

A survey of flavones reported in juice and wine is shown in **Table 2**. All of the juices with appreciable flavone concentrations are in the citrus family and contain methylated flavones, e.g., acacetin, diosmetin, and chrysoeriol glycosides. Bergamot juice contains the highest concentrations of total flavone glycosides, including both flavone *O*- and *C*-glycosides (40, 41). Apigenin and diosmetin 6,8-di-*C*-glucosides were found in bergamot, mandarin orange, orange, and citron juices (40). Although kumquats (*Fortunella crassifolia*) contain >21 mg apigenin/100 g fresh weight (50), kumquat juice (*F. japonica*) has <1 mg/100 g (45). This may be due to differences in species or to the amount of peel included in the sample. In grapefruit, peels contained >100 times the concentration of naringin as the juice (51).

The concentrations of flavones in fruits, vegetables, olive oil, and honey are listed in **Table 3**. Most of the studies reported values for aglycones after acid hydrolysis, although some gave concentrations of flavone *O*-glycosides. Fresh parsley had the highest flavone concentrations of the fresh foods, with ≤1484 mg apigenin/100 g (60). Chicory had ≤333 mg luteolin/100 g in one study (14), but luteolin was not detected in another (62). Wide variations in flavone concentrations between studies were also observed for many other fresh foods. Vegetables with the highest concentrations were in the sunflower family (Asteraceae) and carrot family (Apiaceae).

The concentrations of flavones in cereals and legumes are listed in **Table 4**. Millet and sorghum provided the highest concentrations of flavones of all cereals and legumes, providing 15 mg apigenin and 35 mg luteolin/100 g millet and ≤29 mg apigenin and 18 mg luteolin/100 g sorghum. Although these levels are lower than those seen in other foods, such as parsley, celery and chicory, it is important to consider the flavone concentrations in these foods. Some areas of the world, including Africa and some Asian countries, consume very high amounts of these grains; thus, millet and sorghum can contribute substantially to flavone intake (91). However, reported amounts were variable, with no flavones detected in some cases.

Effects of processing on flavone glycosides

As with other flavonoids, flavones are typically present in plants as glycosides. Flavone *O*-glycosides are composed of the aglycone moiety, with ≥1 sugar attached with a β linkage (Figure 1). These compounds may be modified slightly by endogenous enzymes, such as malonyl esterases (e.g., conversion from malonylapiin to apiin) (92), but remain as glycosides after processing such as shredding (63), juicing (69, 92), and heating (43). Flavone *C*-glycosides are reportedly stable to fermentation (33), as well as juicing, concentration, spray

TABLE 1 Concentrations of flavones in teas and dry herbs (2 g dry material/serving)

Botanical name (family)	Common name	Flavone	Flavone, mg/100 g dry weight	Flavone, mg/serving	Reference
Chamaemelum nobile (Asteraceae)	Roman chamomile flowers	Apigenin *O*-glycosides	2531	51	27
		Apigenin	395	8	
		Luteolin *O*-glycosides	81	1	
		Luteolin	56	1	
Matricaria chamomilla (Asteraceae)	Chamomile flowers	Apigenin *O*-glycosides	5010–5320	100–106	28
Petroselinum crispum (Apiaceae)	Parsley	Apigenin/apigenin *O*-glycosides	1200–1350	24–27	29, 30
		Luteolin	19.8	<1	
Tanacetum vulgare (Asteraceae)	Tansy leaf	Apigenin	165	3	31
		Luteolin	848	17	
Aspalathus linearis (Fabaceae)	Rooibos/red bush tea	Apigenin *C*-glycosides	46–116	1–2	32–34
		Luteolin *C*-glycosides	172–591	3–12	
Trigonella foenum-graecum (Fabaceae)	Fenugreek seed	Apigenin	731	15	31
		Luteolin	512	10	
Mentha x *piperita* (Lamiaceae)	Peppermint	Apigenin *O*-glycosides	<5.6–27	<1	35, 36
		Luteolin *O*-glycosides	42–3070	1–61	
Origanum vulgare (Lamiaceae)	Oregano	Apigenin	15.6–19.4	<1	30
		Luteolin	901–1137	18–23	
Perilla frutescens (Lamiaceae)	Shiso	Apigenin *O*-glycosides	280–920	6–18	37
		Luteolin *O*-glycosides	30–790	1–16	
Rosmarinus officinalis (Lamiaceae)	Rosemary	Apigenin	43.8	1	31, 38
		Luteolin/luteolin *O*-glycosides	10–661	0–13	
		Diosmetin *O*-glycosides	ND[1]–250	<1–5	
Salvia officinalis (Lamiaceae)	Sage	Luteolin/luteolin *O*-glycosides	49.6–1110	1–22	31, 36
Camellia sinensis (Theaceae)	Green tea	Apigenin *C*-glycosides	47.8–246.8	1–5	20
		Luteolin *C*-glycosides	2.5–21.9	<1	
Camellia sinensis (Theaceae)	Black tea	Apigenin *C*-glycosides	41.4–175.7	1–4	20
		Luteolin *C*-glycosides	5.9–14.0	<1	
Camellia sinensis (Theaceae)	Oolong tea	Apigenin *C*-glycosides	198.6	4	20
		Luteolin *C*-glycosides	14.8	<1	

[1] ND, not detected/limit of detection not specified (38).

drying, and pasteurization (43, 93). Substantial degradation of flavone *C*-glycosides, however, was found after processing for 15 min at 121°C or 4 min at 135°C (93). Compared with most other flavonoid glycosides, flavones are very stable. For example, flavonol *O*-glycosides can be enzymatically hydrolyzed during shredding, heat processing, or fermentation (63, 94), and anthocyanins and isoflavones can be degraded during thermal processing (95, 96). Flavanone

TABLE 2 Concentrations of flavones in juices and wines

Botanical name (family)	Common name (serving size, mL)	Flavone	Flavone, mg/100 g fresh weight	Flavone, mg/serving	Reference
Citrus bergamia (Rutaceae)	Bergamot juice (250)	Apigenin *C*-glycosides	3.8–7.2	10–18	40, 41
		Apigenin *O*-glycosides	6.1–7.7	15–19	
		Luteolin *C*-glycosides	0.6–0.8	2	
		Chrysoeriol *C*-glycosides	1.3–1.5	3–4	
		Chrysoeriol *O*-glycosides	5.4–6.9	14–17	
		Diosmetin *C*-glycosides	2.9–5.9	7–15	
		Diosmetin *O*-glycosides	1.9–2.7	5–7	
Citrus deliciosa (Rutaceae)	Mandarin orange juice (250)	Apigenin *C*-glycosides	2.3–2.7	6–7	40
		Diosmetin *C*-glycosides	0.6–0.8	2	
Citrus medica (Rutaceae)	Citron juice (250)	Apigenin *C*-glycosides	0.6–0.8	2	40
		Diosmetin *C*-glycosides	6.1–6.8	15–17	
Citrus sinensis (Rutaceae)	Orange juice (250)	Apigenin *C*-glycosides	1.0–8.0	3–20	40, 42–44
		Apigenin *O*-glycosides	0.2–0.7	1–2	
		Luteolin *C*-glycosides	0.2–0.5	1	
		Chrysoeriol *C*-glycosides	0.2	1	
		Diosmetin *C*-glycosides	0.2–0.5	1	
Fortunella japonica (Rutaceae)	Kumquat juice (250)	Acacetin *O*-glycosides	0.1	<1	45
		Acacetin *C*-glycosides	0.1	<1	
		Apigenin *C*-glycosides	<0.1	<1	
Vitis vinifera (Vitaceae)	Red and white wine (100)	Apigenin	<0.1[1]–0.6	<1	30, 46–49
		Luteolin	<0.1[1]–0.4	<1	

[1] Limit of detection ranged from 0.00148 to 0.02 mg/100 g fresh weight (46–48).

TABLE 3 Concentrations of flavones in fruits, vegetables, olive oil, and honey

Botanical name (family)	Common name (serving size, g)	Flavone	Flavone, mg/100 g fresh weight	Flavone, mg/serving	Reference
Actinidia deliciosa (Actinidiaceae)	Kiwi fruit (100)	Luteolin/luteolin glycosides	<1.2[1]–2.2	<1–2	30, 50, 52, 53
Spinacia oleracea (Amaranthaceae)	Spinach (200)	Apigenin	<0.1[2]	<1	30, 54–58
		Luteolin	<0.1[3]–6.6	<1–13	
Petroselinum crispum (Apiaceae)	Parsley (5)	Apigenin	<2.4[4]–1484	<1–74	9, 30, 50, 57–60
		Luteolin	<0.4[4]–22	<1–1	
Apium graveolens var. *dulce* (Apiaceae)	Celery stalks (200)	Apigenin	1.3–10.8	3–22	9, 30, 52, 61
		Luteolin	<1.2–2.2	<2–4	
	Celery hearts (200)	Apigenin	19.1	38	30
		Luteolin	3.5	7	
Apium graveolens var. *secalinum* (Apiaceae)	Chinese celery (200)	Apigenin	24.0	48	30
		Luteolin	34.9	70	
Lactuca sativa (Asteraceae)	Lettuce (100)	Apigenin	<0.7[5]–2.7	<1–3	15, 30, 52, 54–58, 62–65
		Luteolin	<1.2[6]–8.8	<1–9	
Cynara scolymus (Asteraceae)	Artichoke heads (200)	Apigenin/apigenin glycosides	3.9–18.9	8–38	30, 66–70
		Luteolin/luteolin glycosides	2.3–7.5	5–15	
Chicorium intybus (Asteraceae)	Chicory leaves (100)	Apigenin/apigenin *O*-glycosides	<0.1–68	<1–68	14, 30, 62, 71
		Luteolin/luteolin *O*-glycosides	<0.1–333	<1–333	
Brassica napus var. *napobrassica* (Brassicaceae)	Rutabaga (200)	Apigenin	<0.1–15.4	<1–31	30, 56
		Luteolin	<0.1	<1	
Brassica oleracea (Brassicaceae)	Broccoli (200)	Luteolin/luteolin glycosides	<0.4[4]–7.5	<1–15	30, 50, 55, 58, 72
Brassica oleracea var. *acephala* (Brassicaceae)	Kohlrabi (200)	Luteolin	ND[7]–1.3	<1–3	30, 58
Brassica rapa var. *chinensis* (Brassicaceae)	Chinese cabbage (200)	Apigenin	<0.1–4.5	<1–9	15, 30, 54, 55, 58, 65
		Luteolin	<0.1–1.2	<1–2	
Citrullus lanatus (Cucurbitaceae)	Watermelon (200)	Luteolin	<1.2[8]–1.8	<2–4	30, 52, 53, 57, 73
Cucumis melo (Cucurbitaceae)	Muskmelon (200)	Luteolin	<1.2[8]–2.6	<2–5	30, 52, 53
Cucirbota sp. (Cucurbitaceae)	Pumpkin (200)	Luteolin	<0.1–1.6	<1–3	30, 53, 72
Vaccinium sp. (Ericaceae)	Blueberry (100)	Luteolin	<1.2–1.8	<1–2	9, 30, 52, 55
Pisum sativum (Fabaceae)	Peas (100)	Apigenin	<0.1[2]–17.6	<1–18	30, 55, 72
		Luteolin	<0.1–0.4	<1	
Olea europaea (Oleaceae)	Black olives (50)	Apigenin	6.5	3	30, 74
		Luteolin	3.2–17.5	2–9	
Olea europaea (Oleaceae)	Green olives (50)	Luteolin	0.2–1.2	<1–1	30
Olea europaea (Oleaceae)	Olive oil (15)	Apigenin	<0.1–0.2	<1	30, 75
		Luteolin	<0.1–0.7	<1	
Citrus paradisi (Rutaceae)	Grapefruit (200)	Apigenin/apigenin glycosides	<0.3[5]–4.9	<1–10	30, 50, 52, 53, 55
		Luteolin	<1.2–1.4	<1–3	
Citrus sinensis (Rutaceae)	Orange (200)	Luteolin	<0.1–1.5	<1–3	30, 53, 55, 76
Fortunella crassifolia (Rutaceae)	Kumquat (100)	Apigenin glycosides	21.9	22	30, 50
Capsicum annuum (Solanaceae)	Bell peppers (100)	Luteolin/luteolin glycosides	0.1–12.9	<1–13	9, 30, 50, 58, 62
Vitis sp. (Vitaceae)	Grapes (200)	Luteolin	<0.1–2.6	<1–5	9, 30, 53, 55, 56
	Honey (20)	Apigenin	<0.1–29.3	<1–6	30, 77–82
		Luteolin	<0.4[9]–3.2	<1–1	

[1] Limit of detection ranged from 0.212 to 1.2 mg/100 g fresh weight (50, 52).
[2] Limit of detection ranged from 0.01 to 0.1 mg/100 g fresh weight (55, 56).
[3] Limit of detection ranged from 0.03 to 0.1 mg/100 g fresh weight (55, 56).
[4] Limit of detection not specified but estimated with the use of the lowest reported value (58).
[5] Limit of detection ranged from 0.01 to 0.67 mg/100 g fresh weight (52, 55, 56, 64).
[6] Limit of detection ranged from 0.3 to 1.2 mg/100 g fresh weight (52, 55, 56).
[7] ND, not detected/limit of detection not specified.
[8] Limit of detection ranged from 0.1 to 1.2 mg/100 g fresh weight (52, 73).
[9] Limit of detection not specified but estimated with the use of the lowest reported value (78).

TABLE 4 Concentration of flavones in cereals and legumes (28 g dry grain or legume/serving)

Botanical name (family)	Common name	Flavone	Flavone, mg/100 g dry weight	Flavone, mg/serving	Reference
Pisum sativum (Fabaceae)	Field pea	Apigenin *C*-glycosides	<0.3[1]–4.6	<1–1	83
		Luteolin *C*-glycosides	<0.1[1]–1.1	<1	
		Luteolin *O*-glycosides	<1.6[1]–4.6	<1–1	
Cicer arietinum (Fabaceae)	Chickpea	Luteolin *C*-glycosides	<0.1[1]–0.1	<1	83
Vicia faba (Fabaceae)	Fava bean	Apigenin *C*-glycosides	<0.3[1]–0.5	<1	30, 83
		Apigenin *O*-neohesperidoside	<0.3[1]–0.3	<1	
		Luteolin *C*-glycosides	<0.1[1]–0.9	<1	
Digitaria exilis (Poaceae)	Millet, fonio	Apigenin	15.0	4	84
		Luteolin	35.0	10	
Sorghum bicolor (Poaceae)	Lemon-yellow sorghum	Apigenin	0.1–28.7	<1–8	85
		Luteolin	0.3–7.5	<1–2	
Sorghum bicolor (Poaceae)	Red sorghum	Apigenin	<0.2–20.4	<1–6	30, 85, 86
		Luteolin	<0.2–18.2	<1–5	
Triticum monococcum (Poaceae)	Wheat grain	Apigenin *C*-glycosides	2.1	<1	87
Triticum urartu (Poaceae)	Wheat grain	Apigenin *C*-glycosides	3.8	1	
Triticum dicoccum (Poaceae)	Wheat grain	Apigenin *C*-glycosides	9.5	3	
Triticum carthlicum (Poaceae)	Wheat grain	Apigenin *C*-glycosides	10.5	3	
Triticum polonicum (Poaceae)	Wheat grain	Apigenin *C*-glycosides	7.4	2	
Triticum turgidum (Poaceae)	Wheat grain	Apigenin *C*-glycosides	12.7	4	
Triticum durum (Poaceae)	Wheat grain	Apigenin *C*-glycosides	7.8	2	
Triticum spelta (Poaceae)	Wheat grain	Apigenin *C*-glycosides	17.9	5	
Triticum aestivum (Poaceae)	Wheat grain	Apigenin *C*-glycosides	8.0	2	
Oryza sativa (Poaceae)	Black rice	Apigenin *C*-glycosides	6.3	2	88
		Luteolin *C*-glycosides	1.4	<1	
	Red rice	Apigenin *C*-glycosides	0.7	<1	
		Luteolin *C*-glycosides	0.7	<1	
	Brown rice	Apigenin *C*-glycosides	1.8	<1	
		Luteolin *C*-glycosides	0.3	<1	
	White rice	Apigenin *C*-glycosides	1.6	<1	
		Luteolin *C*-glycosides	0.8	<1	
Fagopyrum esculentum (Polygonaceae)	Dehulled, roasted buckwheat	Apigenin *C*-glycosides	0.2–0.7	<1	30, 89
	Whole buckwheat	Apigenin *C*-glycosides	0.3–3.3	<1	90
		Luteolin *C*-glycosides	0.2–3.4	<1–1	

[1] Limit of detection not specified but estimated with the use of the lowest reported value (83).

O-glycosides, however, are fairly stable during heat processing (43).

Absorption and metabolism of flavone *O*-glycosides

Given that dietary flavones are ingested predominantly as glycosides, their fate is determined by how and where they are absorbed, metabolized, transported, and excreted. The absorption of orally delivered flavone *O*-glycosides and aglycones has been the subject of many animal studies, particularly in rats. Most of these rat studies show that apigenin, luteolin, and their simple glucosides are absorbed quickly. The time of maximum plasma concentration (T_{max})[3] was generally ≤1 h, with a maximum plasma concentration (C_{max}) of 1–100 μmol/L (97–100), depending on the dose and the type of food coconsumed (food matrix). The shortest T_{max} values were seen with pure luteolin dissolved in DMSO/polyethyleneglycol, propyleneglycol, or ethanol (97–99), suggesting that the absence of a food matrix speeds absorption. A longer T_{max} was seen with luteolin and apigenin from *Verbena officinalis* extract, and, although the flavone form was not specified (12), the native forms are flavone mono- and diglucuronides (101), which would need to be hydrolyzed to aglycones before absorption. The longest T_{max} and greatest C_{max} was seen in rats fed radiolabeled apigenin, in which the values included all metabolites of apigenin detected as radioactivity (102), and not just the forms typically measured by HPLC. Limited studies have evaluated the absorption of flavones in mice (103, 104), but showed very low plasma flavone concentrations (<1 μmol/L) relative to rats after feeding.

In contrast to pharmacokinetic studies of flavones in rats, those in humans show plasma concentrations of <1 μmol/L after consumption (**Table 5**). Many human studies used celery leaves or parsley as their flavone source (105–108), which contain primarily flavone apiosylglucosides (29, 114). Although an older study that used HPLC-UV did not find flavones in serum (107), 2 newer reports that used HPLC–electrochemical detection found concentrations averaging <0.2 μmol/L with T_{max} values of >7 h (105, 108). The latter suggests that the flavone apiosylglucosides are

[3] Abbreviations used: CBG, cytosolic β-glucosidase; C_{max}, maximum plasma concentration; T_{max}, time of maximum plasma concentration; UGT1A, UDP glucuronosyltransferase family 1 member A.

TABLE 5 Bioavailability of flavone *O*-glycosides in humans[1]

Source	Subjects, *n*	Dose	Intervention duration	Plasma T_{max}, h	Plasma concentration, mol/L	AUC	Urinary excretion, % of intake	Elimination half-life, h	Reference
Parsley	6 men and 5 women	2 g parsley/kg body weight (0.24 mg apigenin/kg body weight)	Single dose	7.2	0.127	61.98 min · $\mu mol^{-1} \cdot L^{-1}$	0.22	—	105
Parsley	7 men and 7 women	20 g parsley/d (4.5 mg apigenin/d)	7 d	—	—	—	0.58	—	106
Parsley	9 men and 9 women	4.9 g dried parsley/d (84 mg apigenin/d)	7 d	—	<1.1	—	—	—	107
Celery leaf	10 men and 10 women	2 g celery leaf/kg body weight (apigenin dose unknown)	Single dose	7.70	0.190	89.02 min · $\mu mol^{-1} \cdot L^{-1}$	—	—	108
40 mL chamomile extract (ethanol/water)	1 woman	90.2 mg apigenin 7-glucoside, 4.2 mg luteolin 7-glucoside, 6.1 mg apigenin, 2.4 mg luteolin	Single dose	—	<0.74	—	ND	—	109
Extract of *C. morifolium* tablets	4 men and 4 women	85.56 mg luteolin 65.04 mg apigenin	12 h	—	—	—	2.30 luteolin 6.09 apigenin (12 h)	—	110
Cooked artichoke heads (61.7 g)	2 men and 3 women	4.9 mg luteolin glycoside 6.0 mg apigenin glycoside	Single dose	—	ND	—		—	67
Artichoke leaf extract	7 men and 7 women	14.4 or 35.2 mg luteolin eq.	Single dose	0.36 or 0.46	0.206 or 0.546	168.6 or 499.6 ng · $h^{-1} \cdot mL^{-1}$	1.72 or 1.99	2.50 or 2.45	111
Diosmin (diosmetin 7-*O*-rutinoside)	1 man	1000 mg (493 mg diosmetin eq.)	Single dose	3.00	0.170	142.84 ng · $h^{-1} \cdot mL^{-1}$	0.003	1.10	112
Diosmin	2 men and 3 women	10 mg diosmin/kg body weight (4.93 mg diosmetin eq./kg body weight)	Single dose	1	1.388	5617 ng · $h^{-1} \cdot mL^{-1}$	ND	31.5	113

[1] eq., equivalent; ND, not detected/limit of detection not specified; T_{max}, time of maximum plasma concentration.

absorbed in the colon, which may contribute to their low bioavailability. The colon has less surface area for absorption and is also a site for extensive metabolism and degradation by gut microbiota, as will be discussed later. Subjects who consumed comparable amounts of flavones as simple glucosides from artichoke leaf extract had T_{max} values of <1 h and maximal plasma concentrations of 0.2–0.5 μmol/L (111). Whereas <1% of flavones from parsley were found in urine (105, 106), after the consumption of aglycone-rich hydrolyzed *Chrysanthemum morifolium* extract, urinary excretion was 2% of luteolin and 6% of apigenin intake (110).

Although numerous studies have shown that flavones are absorbed systemically (Table 5), they are typically found in plasma or urine as glucuronide or sulfate metabolites, rather than the original flavone *O*-glycosides (111, 113, 115). As with many other flavonoid glycosides in foods, flavones must first be hydrolyzed to aglycones for absorption (116), and are then metabolized to glucuronidated or sulfated forms before reaching systemic circulation (117). A brief summary of the sites of metabolism and enzymes involved is presented in **Table 6**.

It is not clear what role the stomach plays in the absorption of flavones in humans. Although few compounds are absorbed in the human stomach because of its relatively small surface area (122), ex vivo models show that flavonoid glycosides can be absorbed through the human stomach and cleaved by stomach-specific β-glucosidase (123). Rapid absorption, rapid elimination, and poor absorption efficiency are considered to be consistent with absorption in the stomach, and anthocyanins are among the flavonoids that fit this description (3). Human clinical trials with flavones, although limited, suggest that they might behave in a similar manner. Whereas studies that collected plasma samples starting 4 h after dosing found T_{max} values of >7 h for apigenin (105, 108), T_{max} values of <0.5 h were obtained when blood collection was begun 0.25 h after dosing (111). It is possible that rats have a greater ability to absorb flavones through the stomach lumen, and there is evidence that flavone glycosides can be absorbed there (124), which would provide an explanation for the higher levels of flavone absorption seen in rats.

The small intestine, which is longer than the stomach and contains villi and microvilli, is much more effective at absorbing compounds (122). There is also evidence that the small intestine is a major site of hydrolysis and metabolism of flavone *O*-glycosides. Cleavage of flavonoid glycosides by β-glucosidase in the small intestine was tested in vitro with a Caco-2 model and cultured small intestinal cells from 10 people. The human small intestinal cells showed ≤87-fold interindividual variation in β-glucosidase activity, with variation also depending on the flavonoid conjugate being hydrolyzed (116). Two β-glucosidases in small intestinal cells can cleave flavonoid glycosides, with the greatest effect on flavonol, flavone, flavanone, and isoflavone *O*-glucosides (116, 118). The most likely to act on flavone glycosides in the small intestine is lactase-phlorizin hydrolase, a membrane-bound enzyme. Of the various flavonoids tested, it cleaved glucose but did not hydrolyze rhamnose, xylose, arabinose, and galactose to yield aglycones (116). Lactase-phlorizin hydrolase also hydrolyzes lactose, and is therefore not produced in lactose-intolerant individuals; this is a possible source of interindividual variation (116).

The second glucosidase found in intestinal cells is cytosolic β-glucosidase (CBG), which also resides in the cytosol of human liver, spleen, and kidney cells. It has been shown to preferentially hydrolyze β-D-fucose, β-D-glucose, α-L-arabinose, and β-D-galactose in vitro, but it can also hydrolyze β-L-arabinose and β-D-xylose linkages (118). In order for CBG to cleave flavonoid glycosides, the molecules must first be actively or passively transported into the cytosol. Although it has been proposed that flavonoids such as quercetin are transported into cells by passive diffusion (125), this would favor the transport of less polar (e.g., aglycone) molecules through the lipid bilayer membrane. And although the sodium-dependent glucose transporter 1 is involved in the uptake of some flavonoid glucosides such as quercetin 3-glucoside and 4′-glucoside (126), it does not appear to transport flavones and, in fact, may be inhibited by luteolin (127). Therefore, flavone *O*-glycosides must be cleaved to aglycones before they are absorbed into the small intestinal epithelial cells, and CBG does not play a role in their deglycosylation.

Flavones may be metabolized in the small intestine, and if flavones and their metabolites are transported to the basolateral side of the small intestine, they are carried to the liver via the hepatic portal vein (122). As with other flavonoids, flavones are metabolized by phase II enzymes in both the small intestine and liver. They are extensively metabolized by intestinal cells to glucuronidated and sulfated forms and then effluxed back to both the intestinal lumen and the bloodstream. The efflux of apigenin sulfate is mediated by both multidrug resistance–related proteins and organic anion transporters, whereas the efflux of apigenin glucuronide is mediated by multidrug resistance–related proteins. This efflux of flavone metabolites is likely a rate-limiting step in transport across the intestinal membrane (117).

TABLE 6 Most common metabolic conversions of flavone *O*-glycosides[1]

Site of metabolism	Enzyme	Conversion	Reference
Small intestine	β-glucosidase (LPH)	Flavone 7-*O*-glucoside to aglycone	118
Small intestine, liver	UGT1A1, UGT1A8, and UGT1A9	Aglycone to flavone glucuronide	119
Liver	SULT1A1 and SULT1E1	Aglycone to flavone sulfate	103, 120, 121
Large intestine	Intestinal microbiota	Flavone 7-*O*-glucoside to aglycone, 3-(4-hydroxyphenyl) propionic acid	100

[1] LPH, lactase-phlorizin hydrolase; SULT1, sulfotransferase 1; UGT1A, UDP glucuronosyltransferase family 1 member A.

In vitro studies with human liver and intestinal microsomes found that luteolin was glucuronidated primarily at the 7 position in liver cells and at the 3′ and 4′ positions in intestinal cells. This differed markedly from rats, in which liver microsomes glucuronidate luteolin primarily at the 3′ position. Intestinal microsomes conjugated nearly 3 times as much luteolin as liver microsomes. When individual enzymes were tested, some glucuronidated luteolin much more efficiently than others, with human UDP glucuronosyltransferase family 1 member A (UGT1A) 1, UGT1A8, and UGT1A9 being especially effective (119). When apigenin was incubated with microsomes and cytosol isolated from human liver and intestinal tissue, monoglucuronides were produced by microsomes and monosulfates were produced in the cytosol. Apigenin was more rapidly glucuronidated than sulfonated (103). Another study that used HEPG2 human liver cells found that luteolin absorbed into the cells was predominantly methylated, indicating catechol-*O*-methyltransferase activity, which was not observed with apigenin (120). Evidence of catechol-*O*-methyltransferase activity for luteolin but not apigenin has also been observed in rats (128, 129). Based on these observations, future analytic methods will need to include methylated metabolites of luteolin, such as chrysoeriol and diosmetin, because they are not typically converted to luteolin during sample preparation.

Flavonoids that reach the colon can be further hydrolyzed and metabolized by bacteria. Rats were either kept germ free or associated with human intestinal microbiota. After giving the rats apigenin via an intragastric 7-glucoside dose, different levels of apigenin, apigenin conjugates, and other metabolites were excreted in the urine and feces (100). Rats with human intestinal microbiota excreted primarily conjugated apigenin and free 3-(4-hydroxyphenyl)propionic acid in the urine and free apigenin in feces compared with conjugated apigenin in the urine and free and conjugated apigenin in the feces of germ-free rats. Rats with human intestinal microbiota excreted more of the following metabolites in their urine: free and conjugated naringenin, free phloretin, conjugated luteolin, free 3,4-dihydroxyphenylpropionic acid, free and conjugated 3-(4-hydroxyphenyl)propionic acid and 4-hydroxycinnamic acid, and free 3-hydroxyphenylpropionic acid (100). It is interesting to note that luteolin and naringenin were also found in germ-free rats, indicating that they may be products of metabolism by the rats themselves. The metabolism of apigenin to luteolin has previously been reported in rats, mediated by the phase I enzyme cytochrome P450 (130), and this conversion has also been demonstrated in human liver microsomes (131). To our knowledge, no other studies have reported naringenin as a metabolite of apigenin, but it can be detected in samples if unpurified β-glucuronidase from *Helix pomatia* is used in the sample preparation (132).

In vitro experiments with *Eubacterium ramulus*, an obligate anaerobe found in the human colon, showed that eriodictyol and 3-(3,4-dihydroxyphenyl)propionic acid were metabolites of luteolin (133). Studies with *Clostridium orbiscindens*, which is found in numbers similar to those for *E. ramulus* in the intestinal tract, also showed that eriodictyol was a product of luteolin metabolism and that naringenin was a product of apigenin. Phloretin, 3-(4-dihydroxyphenyl) propionic acid, and phloroglucinol were end products of both apigenin and luteolin degradation (134).

Absorption and metabolism of flavone *C*-glycosides

As with for flavone *O*-glycosides, rats are the most common animal model used for flavone *C*-glycoside absorption. The T_{max} for vitexin (apigenin 8-*C*-glycoside) derivatives was <1 h, and the C_{max} was 1–29 μmol/L, varying with the dose (135–137). Urinary excretion of <1% confirms that flavone *C*-glycosides are poorly absorbed (136), and 10–88% recovery from feces indicates that they may be resistant to degradation by gut bacteria in rats (136, 138). As with flavone *O*-glycosides, the *C*-glycosides are less bioavailable in humans than in rats (**Table 7**). Although metabolites of apigenin or luteolin *C*-glycosides were found in plasma after human subjects drank rooibos tea, the concentrations were <1 nmol/L (34). Gastrointestinal and feces extracts showed 3 primary metabolites by intestinal bacteria: phloroglucinol, hydrocaffeic acid, and phloretic acid (138). When luteolin 6-*C*-glucoside (isoorientin) was incubated with human intestinal bacteria, only a small amount of luteolin aglycone was produced. The most abundant metabolites were 3,4-dihydroxyphenylpropionic acid and eriodictyol, with small amounts of 6-*C*-glucosyleriodictyol and phloroglucinol (140).

Biological activity of flavones in humans

Several intervention studies have been carried out with flavones and flavone-containing foods in humans. A trial that used fresh and cooked parsley as a flavone source found

TABLE 7 Bioavailability of flavone *C*-glycosides in humans[1]

Source	Subjects, *n*	Dose	Plasma T_{max}, h	Plasma concentration, mol/L	Urinary excretion, % of intake	Reference
Rooibos teas (fermented and unfermented leaves)	5 men and 5 women	0.1–0.2 mg luteolin, 12.2–12.6 mg luteolin *C*-glycosides, and 2.0–2.2 mg apigenin *C*-glycosides	—	ND	ND	139
Rooibos tea (unfermented leaves)	10 men	43 mg luteolin *C*-glycosides, 5.9 mg apigenin *C*-glycosides, and 0.9 mg luteolin *O*-glycosides	1.5–3	<0.001	—	34

[1] ND, not detected/limit of detection not specified; T_{max}, time of maximum plasma concentration.

that the treatment group had higher blood antioxidant enzyme activities, including superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase (106). Other interventions with flavone-rich foods showed that they differed in their effects on biomarkers for heart disease and stroke. In a crossover study, subjects showed no differences in platelet aggregation after consuming a dried parsley supplement for 7 d. Although apigenin aglycone appeared effective at doses as low as 2.5 μmol/L in vitro, it did not show an effect at 250 nmol/L (107), which is closer to the concentrations expected in plasma. The metabolism of apigenin aglycone to conjugates might also explain the lack of efficacy. In another study, an 84-d trial that used artichoke leaf extract as an apigenin source found that the treatment group had lower total cholesterol than those taking placebo, but there were no significant differences in HDL cholesterol, LDL cholesterol, or TGs (141). Supplementation with vitexin-rich hawthorn extract lowered total and LDL cholesterol after 6 mo, but also had no effect on HDL cholesterol or TGs (142). Diosmetin rutinoside supplements have been successfully used in Europe to reduce bleeding and improve wound healing (143, 144). The proposed mechanisms of action include increasing venous tone and countering inflammatory mediators (144), congruent with the anti-inflammatory activity of flavones already demonstrated in animal studies.

The efficacy of flavones in human clinical trials cannot always be predicted by in vitro, animal, or bioavailability studies. One reason is that although flavones are found in circulation as glucuronide or sulfate conjugates, most in vitro experiments are done with aglycones or glucoside conjugates. It is possible for neutrophils to deconjugate luteolin glucuronide to aglycone in circulation, releasing the biologically active aglycone (145), but the extent of this process in vivo is unknown. Flavones may also be active in the intestinal lumen rather than in circulation, providing an explanation for the biological activity of the poorly available flavone *C*-glycosides. For example, apigenin and luteolin inhibit TNF-induced proinflammatory gene expression in murine intestinal epithelial cells (146). Similar effects were demonstrated with luteolin in human epithelial cells, indicating potential activity against inflammatory bowel disease (147).

Conclusions

Flavones occur in a wide variety of fruits, vegetables, and beverages. In their native forms, they are found as both *O*- and *C*-glycosides, with *O*-glycosides being more common and usually better absorbed. Relative to other polyphenols, flavones are not well absorbed, with plasma concentrations typically <1 μmol/L in humans. However, flavones have demonstrated many potentially beneficial activities in animal studies and human trials, and these should be further explored. Future clinical trials should not only take into consideration the dose but also the flavone form, because some native glycosides are poorly available and could be improved through processing.

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