Bioavailability and Metabolism of Flavonoids: A Review

Masoumeh Akhlaghi¹*, Sahar Foshati²

1. Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
2. Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

Flavonoids are a group of plant antioxidants that are widely distributed in plants from the root and stem to the leaves, flowers, and fruits. They are generally present as glycosides, conjugated to sugars, although their aglycone forms may also exist. Flavonoid glycosides are hydrolysed from sugar moieties in the intestine. After release from sugars, the flavonoid aglycones undergo conjugation with other molecules to facilitate the excretion and shorten the half-life of flavonoids. Conjugation also reduces the antioxidant and potential pro-oxidant effects of flavonoids. Flavonoids have low intestinal bioavailability and rapid urinary and biliary excretion. However, the bioavailability of flavonoids varies between different kinds of flavonoids. The best rate of absorption among flavonoids is seen in gallic acid and isoflavones, followed by catechins, flavanones, quercetin, proanthocyanidins, and anthocyanins. Quercetin metabolites are excreted very slowly, whereas anthocyanins and catechins are excreted very rapidly. Information on bioavailability and metabolism of flavonoids can help designing the best intervention strategies. In conclusion, flavonoids have low intestinal bioavailability and rapid urinary and biliary excretion. The bioavailability of them varies between different kinds of flavonoids. The most rapid excretion rates belong to anthocyanins and flavanols while the slowest rates are for flavonols.


Introduction
Flavonoids are a subgroup of the more extended family of polyphenols. Polyphenols constitute a widespread group of plant compounds implicated in plants’ wellbeing, growth and reproduction, pigmentation, and protection against micro-organisms and enemies (1). They are widely distributed in plants from the root and stem to the leaves, flowers, and fruits. Their quantities in fruit and vegetables are influenced by numerous factors including light, environmental conditions, plant species, degree of ripeness, germination, processing, and storage. As an example, cherry tomatoes possess six times more quercetin per gram fresh weight than normal size varieties of tomatoes, probably because polyphenols are generally synthesized and stored in the skin, and therefore smaller varieties have a higher skin to volume ratio (2).

Total dietary intake of polyphenols is firmly
dependent on the food culture and the individual food preferences, but has been estimated to be about 1 g/day (3) and that of flavonoids between 2 and 70 mg/day (4). Moreover, it has been reported that 10% of the population and 30-70% of patients with specific diseases consume herbal medicines, which naturally contain considerable amounts of polyphenols (5). There are more than 8000 polyphenolic compounds identified, each with a structure containing at least one phenol which is a hexagon ring (benzene) with a hydroxyl group (6). Based on their chemical structure, polyphenols can be divided into at least 10 different classes, one of the major groups of which is flavonoids (1, 7).

Classification
Flavonoids were discovered in the 1930's when a factor extracted from lemon juice could attenuate vessel permeability and bleeding in scorbutic Guinea pigs where vitamin C was not effective, leading to their nomination as vitamin P, although this terminology was later dismissed (8). More than 5000 flavonoids have been identified (9). The basic structure of flavonoids consists of two benzene rings (A and B) with a pyran ring (C) in the middle (Figure 1). Flavonoids are divided into several subclasses including flavonols, flavanols (including proanthocyanidins), flavanones, flavones, isoflavones, and anthocyanins (1, 7).

Flavonols are represented by quercetin, kampferol, and myricetin (7, 10). They are wide-spread in fruit and vegetables, and may contribute largely to our daily flavonoid consumption. Quercetin, one of the most studied flavonoids, is ingested especially through consumption of tea, onions, red wine, and apples. Flavanols include catechins, which are largely found in green tea (Figure 1). Black tea has far less catechin than green tea due to oxidation of catechins during fermentation. Other major sources of flavanols are chocolate, apples, pears, grapes, and red wine (11).

Proanthocyanidins or condensed tannins (Figure 2) are high-molecular weight oligomers and polymers of catechins, and are the most ubiquitous polyphenols in nature after lignans (12). The major sources of proanthocyanidins in the diet are chocolate, grapes, and apples. Isoflavones, such as genistein and daidzein, are phytoestrogens and may be beneficial in prevention of breast and prostate cancer, menopausal symptoms, cognitive disabilities, osteoporosis, and heart diseases. Soy bean is a rich source of isoflavones (13).

Anthocyanins (Figure 2), such as cyanidin, malvidine, and delphinidin, provide red and purple pigments for fruits. They are abundant in red and black cherries, berries, grapes, and legumes. Consumption of 200 g of black grapes and berries can afford about 1 to 1.5 g anthocyanins (14).

Bioavailability and Metabolism
In nature, flavonoids are generally present as glycosides, conjugated to sugars, although their aglycone forms may also exist (9). The aglycones have stronger antioxidant activity than glycoside forms. The weakening of the antioxidant activity of flavonoids after glycosylation may be due to removing hydroxyl groups by conjugated glycosides, and thereby inhibiting them from scavenging reactive oxygen species (ROS) or chelating transition metals. Furthermore, as glycosylation enlarges the molecule, the passage through membranes may decrease upon glycosylation, leading ultimately to less antioxidant activity. Nonetheless, glycosylation enhances water solubility of the compound and subsequently improves its absorption from the gastrointestinal tract (9).

Flavonoid glycosides can be hydrolysed from sugar moieties by hydrolases at the intestinal brush border or by colonic micro-organisms (7, 15, 16). They may also be transported via a sodium-dependent glucose transporter into enterocytes, where the sugar moieties are removed by β-glucosidases. After release from

Fig. 1: A. Basic structure and numbering system of flavonoids. B. Epicatechin.
sugars, the flavonoid aglycones undergo conjugation reactions involving glucuronidation and sulfation with or without methylation. The conjugations occur in enterocytes and liver, in the latter as a part of detoxification processes. Conjugation facilitates their excretion and thereby shortens their plasma half-life. Almost all flavonoids in plasma and urine are as conjugated forms. Thus, cells in the body are usually exposed to flavonoid metabolites and conjugates rather than aglycones (7, 15, 16).

The conjugates are physically and chemically different from aglycones, and thereby their biologic properties are also different (16, 17). For instance, as the conjugation blocks electron movement over the rings, the conjugated molecules display less potential for redox and therefore antioxidant activity, although this greatly depends on the position of the conjugation. One apparent example of the reduced antioxidant activity resulting from post-absorption structural modification of flavonoids is O-methylation of catechol group in the B ring which remarkably lowers the reactivity potential of the molecule for reaction with ROS (18).

Conjugation is, in fact, one of the defensive mechanisms of the body against flavonoids as pro-oxidants. As flavonoids possess antioxidant activity (19, 20), they might also accompany oxidative consequences (21). By conjugation, the body reduces their antioxidant and potential pro-oxidant effects (22). Flavonoids differ in the magnitude and velocity of absorption and the rate of elimination and plasma half-life (14). The information available on bioavailability and plasma kinetics of flavonoids is greatly variable. Overall, they have low intestinal bioavailability and rapid urinary and biliary excretion, and therefore with a regular diet their plasma concentration rarely exceeds 1 μM (3).

Manach et al. (14) according to the data provided by 97 bioavailability studies in humans suggested that the best rate of absorption among flavonoids is seen in gallic acid and isoflavones, followed by catechins, flavanones, and quercetin glycosides. Gallic acid although has a good absorption, its conjugation with catechins decreases the bioavailability of catechins. Proanthocyanidins and anthocyanins have shown very low bioavailability (14). For instance, the absorption rate of anthocyanins from concentrated black current juice has been found less than 1% (23). However, anthocyanin availability may have been underestimated because of technical complications in measuring anthocyanin metabolites (14).

In contrast to other flavonoids that are separated from their glycosides during the absorption process, anthocyanins appear in plasma in unmodified glycosylated forms, although some glucuronide- and sulphate-conjugated forms in plasma have also been detected (14, 16, 24). Polymerization markedly impairs the absorption of proanthocyanidins (14, 25). Nevertheless, they may be cleaved to smaller units (i.e. monomers, dimers, etc.) by gastric juice or by intestinal microflora, get absorbed, and yield some of the benefits that are currently attributed to proanthocyanidins. Urinary excretion of proanthocyanidin dimers has been reported in rats (26).

Quercetin metabolites are excreted very slowly, having a half-life of 11-28 h in plasma (14), probably due to tight binding to serum albumin (27). This may explain accumulation of quercetin in plasma during long-term supplementation (14). In this way, considerable concentrations of quercetin can be achieved through maintaining a regular diet with moderate amounts of quercetin. Contrarily, anthocyanins and catechins are excreted as rapidly as they are absorbed. For instance, anthocyanins reach the highest levels in plasma within 1-4 h and the maximum level in urine on average 2.5 h after ingestion. Although catechins have shown short plasma half-life and rapid elimination, they may still be capable of accumulating in plasma over a

![Fig. 2: A. Proanthocyanidins. B. Anthocyanins.](image-url)
period of consumption (28), although they are still cleared as quickly as one day after stopping their consumption (29).

*In vitro*, the biological effects of flavonoids are achieved by concentrations (in the micromolar range) higher than those accessible in plasma *in vivo* (mostly in the nonomolar range) (14, 21). However, flavonoid conjugates may bind to some cell receptors or cellular components, resulting in their accumulation after prolonged ingestion (15). Moreover, as flavonoids are hydrophobic, they tend to partition into membranes, resulting in their accumulation and protection from rapid excretion (30).

**Conclusion**

In conclusion, flavonoids have low intestinal bioavailability and rapid urinary and biliary excretion. However, the bioavailability of them varies between different kinds of flavonoids, with isoflavones having the best absorption, followed by flavanols, flavanones, flavonols, proanthocyanidins, and anthocyanins. The most rapid excretion rates belong to anthocyanins and flavanols, while the slowest rates are for flavonols.

**Conflict of Interest**

None declared.

**References**

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