Bioavailability and metabolism of flavonoids

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Summary
Flavonoids are natural polyhydroxylated compounds with proved positive impact on human health. However, majority of the evidence relates to in vitro properties. In literature, attention has been focused on the in vitro mechanism of the flavonoid action, while their metabolic transformations in humans have been almost omitted. Currently, only little information is available on flavonoid bioavailability, formation of conjugates and their bioactivity in humans. It has been established that after flavonoids enter the gastrointestinal tract, the process of absorption in the small intestine takes place. The degree of absorption depends on several factors and differs among the individual flavonoid subclasses. The highest bioavailability has been determined for isoflavones, followed by flavanols, flavanones and flavonol glycosides. Flavonoid glycosides are first deglycosylated prior to the intestinal uptake, whereas aglycones can freely penetrate through cell membranes. Absorbed flavonoids are transported to the liver where they undergo extensive metabolism generating different conjugation forms such as glucuronides, sulphates and methylated derivatives. It has been proposed that these conjugates are responsible for the health-promoting effects of flavonoids. This review provides the latest information on flavonoid research as far as biochemistry, absorption, metabolism and biological activity of flavonoid conjugates in living systems is concerned.

Keywords
flavonoids; absorption; metabolism; conjugates; bioactivity

Flavonoids are secondary metabolites abundantly widespread throughout the plant kingdom. The major sources of flavonoids are fruit products (e.g. citrus fruits, rosehip, apricot, cherry, grapes, black currant, bilberry, apple), vegetables (e.g. onion, green pepper, broccoli, tomato, spinach), beverages (red wine, coffee, tea), cocoa bean, soy products and herbs [1]. They are found in all plant tissues, where they are present inside the cells or on the surfaces of different plant organs.

The chemical structures of this class of compounds are based on a diphenylpropane (C_6-C_3-C_6) skeleton containing two aromatic rings, which are connected through a three-carbon "bridge" and become a part of a six-member heterocyclic ring (Fig. 1). Their structures may range from that of a simple phenolic molecule to that of a complex high-molecular-weight polymer.

Depending on the connection of the aromatic ring to the heterocyclic ring, flavonoids can be divided into three classes: flavonoids (2-phenylbenzopyrans), isoflavonoids (3-phenylbenzopyrans) and neoflavonoids (4-phenylbenzopyrans) [2]. Based on the degree of oxidation and saturation in the heterocyclic C-ring, flavonoids may be divided into several groups which are depicted in Fig. 2 and Fig. 3.

Flavonoids are often hydroxylated in positions 3, 5, 7, 3‘, 4‘ and/or 5‘. One or more of these hydroxyl groups are often methylated, acylated, prenylated or sulphated. In plants, flavonoids are often present as *O*- or *C*-glycosides. The *O*-glycosides have saccharide substituents bound to a hydroxyl group of the aglycone, usually located at position 3 or 7, whereas the *C*-glycosides have saccharide groups bound to a carbon of the aglycone,

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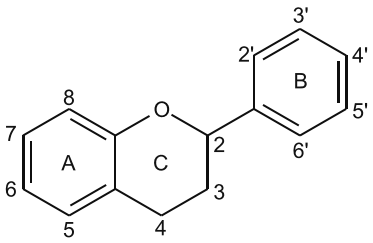

Fig. 1. Basic flavonoid skeleton.

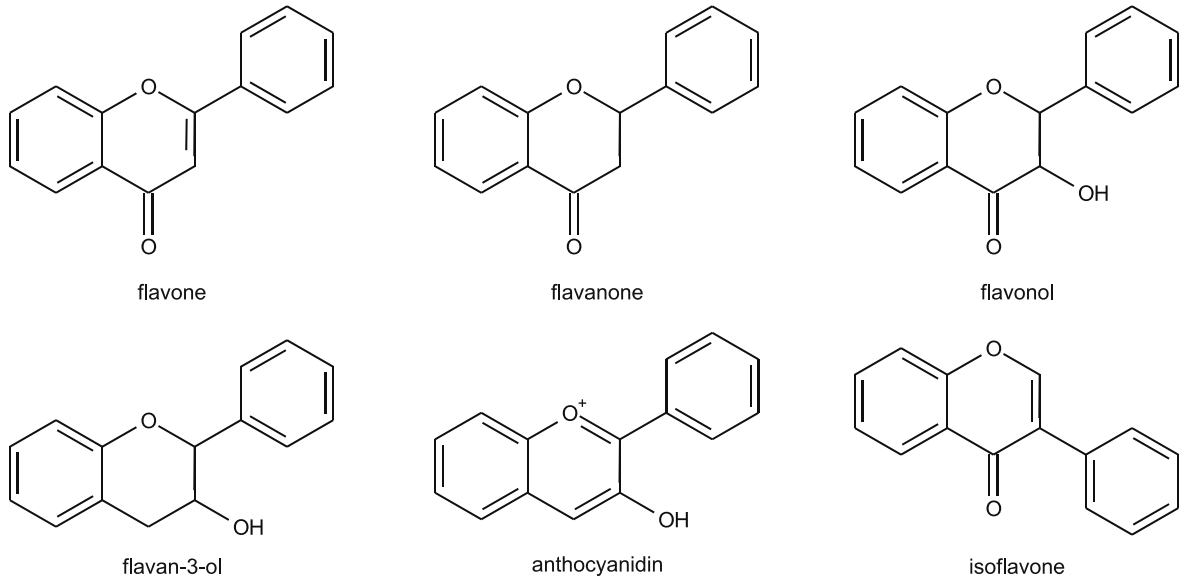

Fig.2. The generic structures of major subclasses of flavonoids.

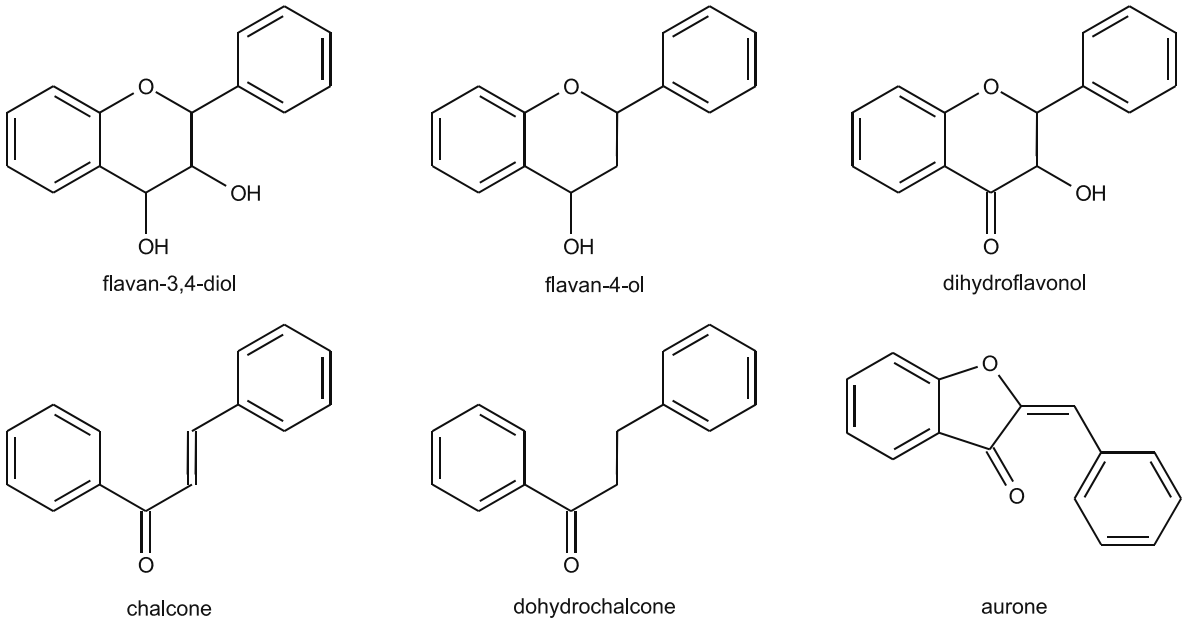

Fig.3. The generic structures of minor subclasses of flavonoids.

usually C6 or C8. The most common saccharides are rhamnose, glucose, galactose and arabinose. Flavonoid diglycosides are also frequently found. The saccharides are often further substituted by acyl residues such as malonate or acetate. Given the above structural variety, it is not surprising that there an extremely large number of flavonoids is recognized [3].

Flavonoids provide various important roles in the plant metabolism, defense, signalling, pathogenesis and symbiosis [4–6]. These compounds are responsible for flower colouring and are involved in response mechanisms against stress, as caused by elevated UV-B radiation [7, 8], infection by microorganisms [9] or animal and insect herbivore attack [10–12]. They are also involved in the nitrogen fixation process and in the plant growth during the reaction with plant growth hormones, principally with auxins and cytokinins [13].

Flavonoids may play an important role in the human and animal diet as long as they affect health. Many epidemiological studies proved the correlation between flavonoid intake and a reduced risk of coronary heart disease, cancer and neurodegenerative diseases [14–24]. The protective effect might be ascribed to their free-radical-scavenging and antioxidant activities [23, 25–28]. In addition, they have been reported to possess antimicrobial [29, 30], antiviral [31–34], anticarcinogenic [23, 34–38], anti-inflammatory [39–41], antiallergic [42, 43] and vasodilatory effects [44, 45]. Flavonoids have also been shown to inhibit lipid peroxidation, platelet aggregation, capillary permeability and fragility, and to affect enzyme systems including phospholipase A2, cyclooxygenase and lipoxygenase [23, 46] as well as ATP-binding proteins, such as mitochondrial ATPase, myosin, protein kinases, topoisomerase II and multidrug-resistance proteins [47, 48].

Many activities of flavonoids were determined using in vitro or ex vivo tests. However, flavonoid transformation in living systems have not been considered in these models. Therefore, the review aims is to describe the bioavailability, absorption and metabolism of flavonoids and their conjugates in vivo.

BIOAVAILABILITY

It seems that there is a great difference between biological properties of flavonoids observed in vitro and their bioactivity in vivo. It is crucial to understand the flavonoid absorption, bioavailability as well as metabolism prior to resolving the question of bioactivity in vivo. The absorption and bioavailability of flavonoids in humans are still controversial.

Different dietary flavonoids show different rates of absorption and bioavailability. Isoflavones are the best absorbed dietary flavonoids, flavanols, flavanones and flavonol glycosides are intermediate, whereas proanthocyanidins, flavanol gallates and anthocyanins are the worst absorbed. However, it is clear that the absorption of dietary flavonoids may be influenced by the matrix in which they are consumed, with enhanced excretion in urine of easily recognized mammalian conjugates observed while presented in the food with a higher fat content [49]. It is not surprising that absorption kinetics vary considerably among different foods, owing to the heterogeneity of saccharides and other functional groups on the flavan nucleus. Absorption is also affected by dosage, vehicle of administration, antecedent diet, sex differences, individual genetic properties and the microbial population of the colon [50, 51].

Absorption

Glycosylated flavonoids

Flavonoids are present in the diet mainly as glycosides and the nature of the saccharide and position of substitution are important factors for intestinal absorption, but the position of the saccharide affects the mechanisms involved in the intestinal uptake [38]. Glycosides need to undergo deglycosylation prior to be absorbed [38, 52–64]. Hydrolysis of the saccharide moiety of flavonoids is carried out by intracellular cytoplasmic β-glucosidase [38, 52, 55, 59, 63, 64]. Three different β-glucosidases have been found in humans: a broad-specificity cytosolic β-glucosidase, lactase phloridzin hydrolase (LPH) and glucocerebrosidase (CBG) [64, 65]. Great differences in β-glucosidase activity may be a critical factor in the bioactivity of flavonoids [55]. Next step after deglycosylation is passive diffusion of the resulting flavonoid aglycone through epithelial cells, which is supported by increased hydrophobicity [38, 64]. However, certain glycosylated flavonoids (e.g. quercetin-4‘-glucoside) were found to be actively transported into epithelial cells via the active sodium-dependent glucose transporter SGLT1 [66].

The absorption of quercetin-4‘-*O*-glucoside appears to follow both ‘LPH/diffusion’ and ‘transport/CBG’ pathways, whereas quercetin-3-*O*-glucoside follows only the ‘LPH/diffusion’ pathway [54]. Rutin (quercetin-3-*O*-rutinoside) is deglycosylated by microfloral rhamnosidases and β-glucosidases present in the colon. Absorption of rhamnoglucosides is delayed and appears to be less efficient [67]. Anthocyanins were considered until recently

that they do not undergo deglycosylation and metabolism as they were found in plasma and urine intact rather than as glucuronate and sulphate conjugates [68, 69]. However, recent evidence suggests that anthocyanins are absorbed and transported in human serum and urine primarily as metabolites, namely, glucuronide and sulphate conjugates [70]. Experiments on flavanones (hesperidin, naringin, narirutin) proved that they also need to undergo hydrolysis of the glycoside moiety prior to the absorption [71]. The intestinal enzymes involved in this reaction are most likely α-rhamnosidases and β-glucosidases [72, 73]. The isoflavones must also first undergo hydrolysis prior to intestinal absorption. KIM et al. [50] studied puerarin and daidzin absorption. These compounds are metabolized by the intestinal microflora to daidzein, which is partially absorbed into the blood [50]. However, MEEZAN et al. [74] reported that puerarin is rapidly absorbed from the intestine without metabolism, while daidzin is hydrolysed to the aglycone. It seems that all main flavonoid glycosides are first hydrolysed to the aglycones prior to intestinal absorption.

Non-glycosylated flavonoids

The only subclass of flavonoids that are present in the non-glycosylated form in the diet are flavan-3-ols. They are the most abundant flavonoids in the human diet, but only little is known about their absorption and metabolism. Although they are found as monomers in the diet, it has been observed that epimerization at C2 may occur during their metabolism [75]. The results on monomers, such as (+)-catechin, (-)-epicatechin and (-)-epigallocatechin (EGC), suggest that these compounds are absorbed mainly in the small intestine, in particular in the jejunum and ileum [76]. In the case of (-)-epigallocatechin gallate (EGCG), the hydrolysis of the gallate moiety prior to absorption has been proposed. The results suggest that EGCG is converted to EGC in the oral cavity, and both catechins are absorbed through the oral mucosa. A catechin esterase activity that converts EGCG to EGC was found in the saliva [77]. Catechins are freely available by passive diffusion, and the mechanism is generally dose-dependent [78]. Due to molecular size, absorption of oligomeric and polymeric flavonoids across the intestinal epithelium requires preliminary degradation to smaller, low-molecular-weight compounds. Procyanidin dimers and trimers are capable of translocating across the small intestinal epithelium. Since these molecules generally consist of (+)-catechin and (-)-epicatechin subunits, it is conceivable that catechins are predominant degradation products [51]. It has been suggested that the depolymerization occurs in the stomach by acid [57]. However, TSANG et al. [79] reported that oligomeric procyanidins were not cleaved into bioavailable monomers at any point during the digestive process of the rat.

Intestinal efflux

Intestinal excretion is an important step that limits the absorption of certain flavonoids [80]. The extent of absorption and bioavailability of drugs has long been known to be affected by various membrane transporters. Members of the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily of transporters including multidrug-resistance protein (MRP), P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are involved in regulating the intestinal efflux of some flavonoids and ultimately influence the net amount that is absorbed into systemic circulation [16, 81, 82]. The activities of these transporters are expected to be important determinants for the pharmacokinetics and pharmacodynamics of flavonoids [82].

The efflux of quercetin and epicatechin metabolites is thought to occur by MRP2, located on the luminal side of epithelial cells [80]. The monocarboxylate transporter P-gp, MRP1 and MPR2 play important roles in the cellular accumulation and potential effects of (-)-epicatechin gallate [83]. The amount of active intestinal efflux of flavonoids representing the major subclasses of flavonoids was studied after in situ intestinal perfusion, where quercetin was excreted the most efficiently, followed by luteolin, eriodicytol and kaempferol, whereas no reaction with efflux transporters was observed in (+)-catechin and (-)-epicatechin [84].

Since ABC transporters are located in cell membranes all over the organism, the interaction between flavonoids and ABC transporters will not only affect the extent of intestinal efflux and bioavailability but also the distribution of flavonoid conjugates to the target sites of action and their elimination. Moreover, bioavailability of different compounds may be increased or decreased at co-administration of flavonoids by a selective interaction with ABC transporters [85].

Metabolism

Flavonoids are well recognized to undergo extensive metabolism prior to the entry into systemic circulation. Absorbed flavonoids are bound to albumin and transported to the liver via the portal vein [86]. Liver is the crucial organ responsible for various biotransformations leading to different conjugated forms of flavonoids. However, the intestinal mucosa, kidney and other tissues are

also involved in the metabolism of flavonoids. The most abundant metabolic transformation reactions of flavonoids are oxidation, reduction, hydrolysis and conjugation with sulphate, glucuronate, or *O*-methylation [60]. DAY et al. [62] suggested that these reactions significantly affect the antioxidant activity of flavonoids and their interactions with proteins. Conjugation reactions with glucuronic acid and/or sulphate seem to be the most common type of metabolic pathways for flavonoids. It seems that the small intestine is the major organ responsible for glucuronidation of many flavonoids. This reaction occurs on the luminal side of the endoplasmic reticulum by uridine-5‘-diphosphate glucuronosyltransferases (UGTs). The process is very fast and even more efficient than cytochrome P450-mediated oxidation [87]. The UGT superfamily of enzymes demonstrates remarkable diversity in substrate recognition and catalyses glucuronidation of a large number of functional groups (e.g., -OH, -COOH, -NH_2, -SH). The UGT1A family is thought to be responsible for glucuronidation of flavonoids [88]. Sulphation and methylation both occur in the cytosol by sulphotransferases (SULTs) and catechol-*O*-methyltransferases [89]. SULT1A1 and SULT1A2 are involved in the sulphation of phenol-type substrates, while SULT1A1 and SULT1A3 were determined to be responsible for (-)-epicatechin sulphation [90].

After absorption and intestinal metabolism, hepatic metabolism of flavonoids takes place. The major products found in the hepatic portal vein are mostly glucuronides and possibly methylated glucuronides. It has been established that these polar conjugates gain access to hepatocytes and are further modified therein. Although quercetin and flavan-3-ol metabolites are clearly able to enter hepatocytes, the mechanism of uptake into hepatocytes is unknown. In the liver, they are further methylated on the catechol ring [91]. Catechin glucuronides formed in the small intestine are subsequently sulphated, as well as methylated [78]. Certain flavonoid glucuronides can be hydrolysed and then re-glucuronidated at a different position, or conjugated with sulphate [91]. Unabsorbed flavonoids can be further degraded by colon microorganisms. A scheme of the metabolism of flavonoid glycosides is presented in Fig. 4 [60].

The fraction of flavonoids that reaches colon can be extensively metabolized by microflora enzymes. This may be an important step in the flavonoid bioavailability, in particular for flavonoids that are not essentially absorbed from the small intestine [47]. Scission of the flavonoid structure can occur as shown in Fig. 5, and this depends on their hydroxylation patterns. The most widespread dietary flavonoids catechin and quercetin, having a 5,7,3‘,4‘-hydroxylation pattern, would enhance ring opening after hydrolysis. Enzymes responsible for the initial ring fission of flavonoids and for demethylation and dehydroxylation of the resulting phenolic acids are, to a great extent, those of intestinal microorganisms. It was found that the ring scission depends on the type and extent of

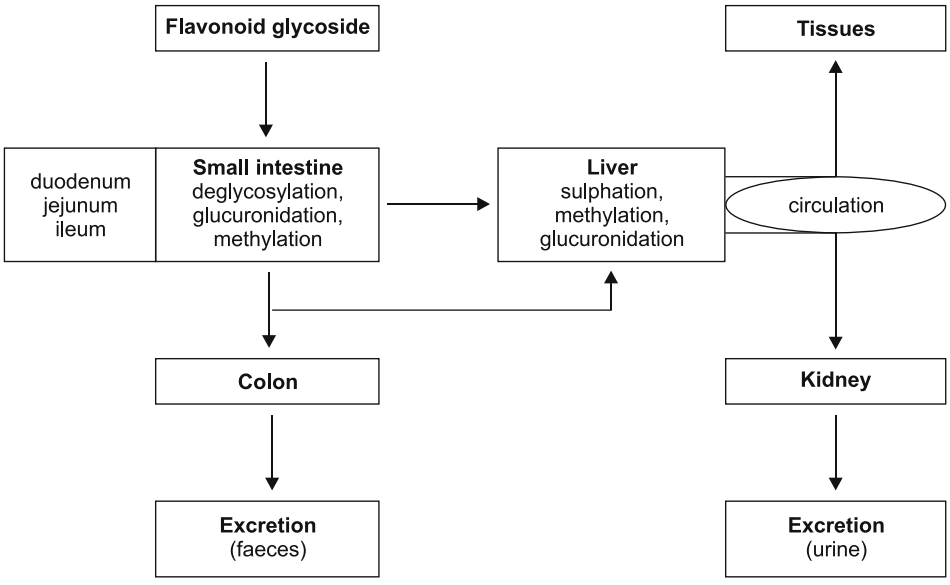

Fig. 4. Metabolism of flavonoids [60].

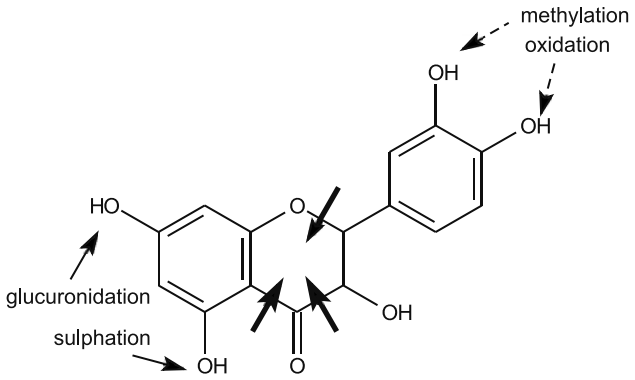

Fig. 5. Potential sites of biotransformation and ring cleavage of flavonoids [60].

oxidation of the carbon atoms of the heterocyclic ring. Another important structural component undergoing biotransformation is the B-ring [60].

Several flavonoids with 3‘,4‘-dihydroxylation in the B ring are excreted in mammalian species as conjugates of their 3‘-*O*-methyl esters. Glucuronide and sulphate conjugates of these methyl esters are major urinary metabolites in man [60]. However, elimination in bile is quantitatively the most important route of elimination for flavonoids. Crespy et al. [84] found that the flavanone eriodicytol has the highest elimination in bile followed by luteolin, kaempferol, quercetin and then (+)-catechin which has minor elimination by this route. The flavonoids eliminated in bile are present as conjugated metabolites.

FLAVONOID METABOLITES AND THEIR BIOLOGICAL EFFECTS IN VIVO

Flavonoids form an integral part of the human diet. Currently there is a broad interest in the effects of dietary polyphenols on human health. An inverse correlation between the intake of certain polyphenols and the risk of cardiovascular disease, cancer and other age-related diseases has been determined in epidemiological studies. The potential beneficial effects of these compounds make them an attractive target for genetic engineering strategies aimed at producing plants with increased nutritional values. Biological properties of flavonoids depend on their bioavailability. Conjugation in the flavonoid metabolism affects properties such as size or mass, charge and hydrophobicity, which may influence their solubility and ability to cross biological membranes. It is also likely to affect their rate of excretion (via kidney or liver) and therefore their half-life in plasma. Conjugation will effectively reduce the number of free hydroxyl groups, which is supposed to alter the antioxidant properties and possibly the ability to interact with important functional cellular proteins including enzymes, receptors and transporters [49]. It is therefore important to determine the impact of these conjugates or metabolites on relevant tissues, cells and proteins in order to provide mechanistic insight regarding the role of flavonoids in protecting against age-related diseases and maintaining optimal health.

Quercetin is one of the most extensively studied polyphenols. It serves as a good example because its metabolism in humans is well understood, and many conjugates of it have been identified [57, 91-96]. More than 95% of the absorbed quercetin was in the form of more than 20 different methylated glucuronated and/or sulphated quercetin conjugates. The main detected metabolites were quercetin diglucuronides in the gut, liver and kidney, and glucuronyl sulphates of methylated quercetin in plasma [92, 97]. The major forms found in plasma were quercetin-3‘-*O*-sulphate (comprising approximately 50% of total quercetin), quercetin-3-*O*-glucuronide, isorhamnetin-3-*O*-glucuronide and quercetin-3‘-*O*-glucuronide [97]. The conjugates and approximate concentrations of common dietary flavonoids present in vivo after oral consumption of a physiologically relevant amount of a common dietary source are summarized in Tab. 1.

The metabolisms of other most abundant dietary flavonoids of humans is comparable in several ways:

1. glycosides are generally not found in plasma or urine in the form ingested,
2. the major forms in plasma and urine are sulphate and glucuronate conjugates of the parent aglycones,

3. methylation may occur on polyphenols that contain orthohydroxy functional groups,
4. aglycones are absent, or constitute only a very small proportion of the total amount of polyphenols present, except for green tea catechins, of which aglycones can constitute a significant proportion of the total amount in plasma [99].

It has been shown that some conjugates of quercetin possess significant antioxidant properties [92, 100], delay lipid peroxidation of cell membranes [101], and reduce Cu^{2+}-induced LDL oxidation [102]. They also exhibit the ability to inhibit lipoxygenase (quercetin-3'-*O*-sulphate) [92], xanthine oxidase (particularly quercetin-4'-glucuronide) [62] and cyclo-oxygenase (isorhamnetin and tamarixetin) in vitro [94]. SAITO et al. [103] reported that quercetin-3-sulphate reduced H_2O_2-induced chromosomal damage in cultured human lymphocytes. Furthermore, quercetin glucuronides were shown to inhibit *N*-acetylation of 2-aminofluroene (a carcinogen) in human acute myeloid HL-60 leukemia cells [104]. LOKE et al. [92] found that at least two of the major in vivo metabolites of quercetin have significant activity for the inhibition of pro-inflammatory eicosanoids such as LTB_4 and PGE_2. Quercetin-3-glucuronide was shown to prevent angiotensin-II–induced vascular smooth muscle cell hypertrophy in cultured rat aortic smooth muscle cells through its inhibitory effects on the JNK and AP-1 signalling pathways [105]. There are some reports suggesting that genistein glucuronides may be active in vivo because they have been shown to have estrogenic activity and can activate human natural killer cells in vitro [106]. Also daidzein sulphoconjugates were found to competitively inhibit sterol sulphatase in hamster liver microsomes [107]. Some glucuronides and sulphates of (+)-catechin and methylated (+)catechin obtained after oral administration of pure (+)-catechin to rats were found to inhibit both generation of reactive oxygen species and binding of U937 monocyte cells to interleukin 1β–stimulated human aortic endothelial cells, whereas (+)-catechin did not do so [108].

Tab. 1. A list of flavonoids and their conjugates found in human plasma and urine (adapted from [98]).

Flavonoid	Conjugates in plasma/rurine	Concentration
Quercetin	Quercetin-3'-sulphate, quercetin-3-glucuronide, isorhamnetin-3-glucuronide and quercetin-3'-glucuronide	0,1–1 $mol.l^{-1}$
Kaempferol	Kaempferol-3-glucuronide and free kaempferol	–
Chrysin	Chrysin-7-sulphate (major) and chrysin-7-glucuronide (minor)	–
Daidzein	Daidzein-7-glucuronide (54%), daidzein-4'-glucuronide (25%), daidzein 7- and 4'-sulphates (13%), daidzein-4',7-diglucuronide (0.4%), daidzein sulphoglucuronides (0.9%), and non-conjugated daidzein (7%)	–
Genistein	Genistein-7-glucuronide, genistein-4'-glucuronide, genistein 7- and 4'-sulphates, genistein-4',7-diglucuronide, genistein sulphoglucuronides, and unconjugated genistein	–
Epicatechin	Non-conjugated epicatechin in plasma (–)-Epicatechin-3'-glucuronide, 4'-methyl-(–)-epicatechin-3'-glucuronide and 4'-methyl-(–)-epicatechin-5 or 7-glucuronide in urine	0,15–0,22 $\mu mol.l^{-1}$
Epigallocatechin	Non-conjugated (–)-epigallocatechin in plasma, 4'-*O*-methyl-epigallocatechin	0,08 $\mu mol.l^{-1}$
Epigallocatechin Gallate	Non-conjugated epigallocatechin gallate in plasma, 4',4''-dimethylepigallocatechin gallate	0,14–0,34 $\mu mol.l^{-1}$
Delphinidin	Unchanged delphinidin glycosides, methylated delphinidin	$pmol.l^{-1}$–$nmol.l^{-1}$
Cyanidin	Unchanged cyanidin glycosides, cyanidin monoglucuronides, methylated cyanidin	$pmol.l^{-1}$–$nmol.l^{-1}$
Malvidin	Unchanged malvidin glycosides, methylated malvidin	$pmol.l^{-1}$–$nmol.l^{-1}$
Petunidin	Unchanged petunidin glucoside, methylated petunidin	$pmol.l^{-1}$–$nmol.l^{-1}$
Peonidin	Unchanged peonidin arabinoside, peonidin monoglucuronides, methylated peonidin	$pmol.l^{-1}$–$nmol.l^{-1}$
Pelargonidin	Unchanged pelargonidin-3-glucoside, pelargonidin monoglucuronides, sulphoconjugate of pelargonidin	–

CONCLUSIONS

Flavonoids represent remarkable plant components. They form a structurally and functionally diverse group of secondary metabolites which are known to possess many important functions in plants, in their growth, development and reproduction, defense against biotic and abiotic stress factors, flower pigmentation and signalling. They have also been reported to provide various beneficial effects to human health. Many epidemiological studies have demonstrated the association between flavonoid intake and a reduction in risk of cancer, cardiovascular and neurodegenerative diseases. Despite quite a big amount of information available on potential health-promoting effects of flavonoids in vitro, only little is known about their physiological mechanism of action and bioactivities in vivo. It is agreed that bioavailability and biotransformation are limiting factors for biological activities in humans, and therefore it is necessary to pay more attention to studies of the effects of flavonoid conjugates. For effective utilization of the current knowledge in the flavonoid research in human nutrition, pharmacy and medicine, future research focussing on the extent of absorption related to the flavonoid structure, pharmacokinetics in humans, characterization of flavonoid metabolites and health effects of these metabolites is necessary.

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