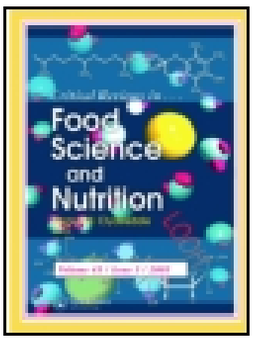

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REVIEW

The fate of flavonoids after oral administration: a comprehensive overview of its bioavailability

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ABSTRACT

Despite advancements in synthetic chemistry, nature remains the primary source of drug discovery, and this never-ending task of finding novel and active drug molecules will continue. Flavonoids have been shown to possess highly significant therapeutic activities such as anti-inflammatory, anti-oxidant, anti-viral, anti-diabetic, anti-cancer, anti-aging, neuroprotective, and cardioprotective, etc., However, it has been found that orally administered flavonoids have a critical absorption disorder and, therefore, have low bioavailability and show fluctuating pharmacokinetic and pharmacodynamic responses. A detailed investigation is required to assess and analyze the variation in the bioavailability of flavonoids due to interactions with the intestinal barrier. This review will emphasize on the bioavailability and the pharmacological applications of flavonoids, key factors affecting their bioavailability, and strategies for enhancing bioavailability, which may lead to deeper understanding of the extent of flavonoids as a treatment and/or prevention for different diseases in clinics.

KEYWORDS

Flavonoids bioavailability enhancement; polyphenol structure and absorption; biofunctions of flavonoids; factors affecting bioavailability of flavonoids

Introduction

Flavonoids, a group of over 6,000 natural polyphenolic compounds, commonly found in medicinal herbs and human diets such as fruits, vegetables, and seeds. Flavonoids play various essential roles in plants, e.g., attract pollinating insects, counteract environmental stresses, microbial infections, and controls cell growth. Due to a large number of associated health benefits ranging from anti-oxidation to anti-tumor, the intake of herbal items and/or healthcare supplements encapsulating various flavonoids has increased due to their nontoxic nature (Xia et al. 2014; Srinivas 2015).

The oral route is the most preferable route for administering flavonoids owing to their widespread nutritional and health benefits, and more recently, flavonoids are used in many preclinical models to enhance the bioavailability of other co-ingested drugs or as a synergistic therapy to reduce the doses of other drugs or increase their sensitivity, such as chemotherapeutic drugs or immunosuppressants. However, the intestinal absorption mostly suffers due to inter-subject variability and various other factors such as physicochemical characteristics, i.e., lipophilicity and solubility, pharmaceutical factors like dosage form, physiologic conditions such as GI emptying rate, pH, intestinal blood supply and metabolic enzymes alongwith expression and function of intestinal transporters, e.g., ABC and SLC as well as metabolic enzymes (CYP 450), which all together affects the stability, solubility and permeability of flavonoids, which ultimately leads to low oral bioavailability, that significantly influence the efficacy and safety of the flavonoids (Oostendorp, Beijnen, and Schellens 2009).

Generally, flavonoids have low bioavailability, which varies depending on their composition, subclass, glycosylation, molecular weight, and esterification. Isoflavones, flavanones, catechins, and quercetin glucosides are better absorbed whereas, condensed tannins, anthocyanins, and galloylated (tea catechins), are the lowest absorbed. Moreover, poor absorption and extensive metabolism are associated with the lower plasma concentrations and distribution of flavonoids. Some flavonoids are rapidly absorbed and appear in plasma, for instance, Tmax for anthocyanins is 15 minutes, whereas some others can be slowly absorbed with Tmax till 11 h like isoflavones (Ichiyanagi et al. 2006). Because, flavonoids concentration in plasma is tightly regulated by binding to serum albumins, which delays their release in the plasma and decreases the amount of unbound flavonoids in the plasma. Furthermore, albumin binding limits oxygen-dependent degradation and prolongs their half-life and biological activity. The prolonged-release maintains a constant rate of flavonoids, which may prevent the distribution of flavonoids at higher concentration to the tissues and thereby reducing the cytotoxicity. For example, dietary flavonoid quercetin intake by humans is from

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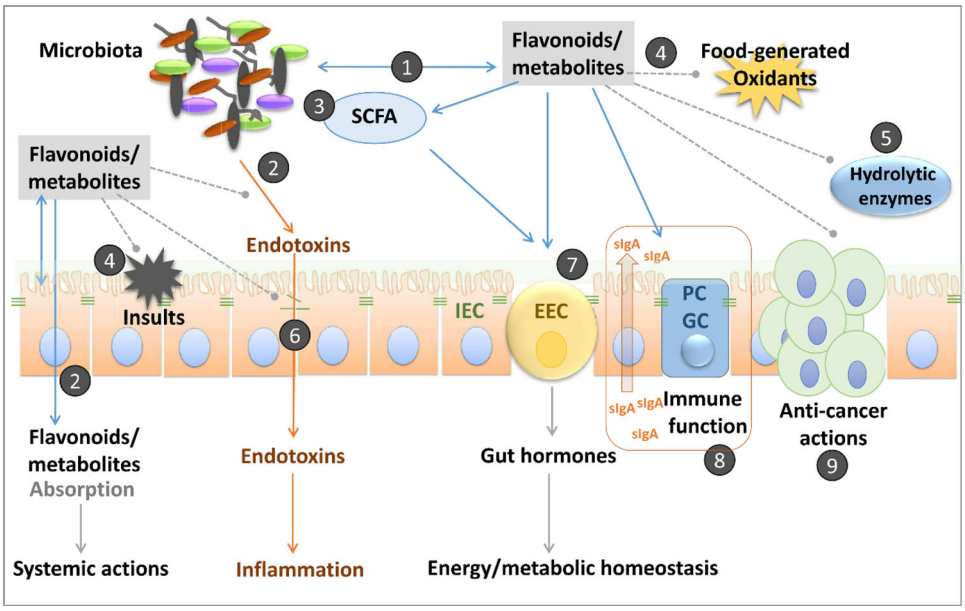

Figure 1. Mechanisms of action of dietary flavonoids at the GI tract. At the GI tract flavonoids/metabolites can (1) positively shape the microbiota, (2) inhibit the production of deleterious endotoxins; and (3) positively modulate the production of beneficial short chain fatty acids (SCFA). Flavonoids/metabolites can exert other beneficial effects at the GI tract by: (4) preventing the harmful effects of food, e.g., oxidants and pharmacological insults; (5) inhibiting the activity of hydrolytic enzymes, e.g., pancreatic lipase, amylase; (6) mitigating intestinal permeabilization and the associated paracellular transport of endotoxins that can initiate local/systemic inflammation; (7) modulating the secretion of gut hormones by entero endocrine cells (EEC) which have both local effects and can systemically modulate energy and metabolic homeostasis; (8) modulating the GI tract immune system, e.g., Paneth cells (PC); and (9), exerting anti-cancer actions. Reproduced from (Oteiza et al. 2018) with permission from B. V Elsevier (Copyright © 2018).

250–500 mg, which may end in < 1% dose (unchanged form), which ultimately enters into the systemic circulation with peak serum levels within range of (~20 nM) (George, Dellaire, and Rupasinghe 2017).

Flavonoids can be either absorbed as parent compounds following conjugation, such as sulfation, methylation, and/or other chemical modifications. Flavonoids can be metabolized by intestinal enzymes at epithelial cells and/or by intestinal microbiota. Generally, three potential metabolic fates of flavonoids exist after ingestion, which decides their molecular and biological functions. Firstly, the parent compounds or metabolites of flavonoids may exert direct effects at the GIT, which may be important to some extent due to the initial higher concentrations at the stomach and upper part of the small intestine. These effects may occur at the epithelial surface in the GIT, immune and endocrine cells, and also at the lumen like direct antioxidant effect. These local effects may play a part in the systemic actions of flavonoids, such as changes in the release of GIT hormones, which influence systemic glucose homeostasis. The second fate can be the interaction of flavonoids with the intestinal microbiota, which results in changes in the microbiota profile, which may include facilitation in beneficial microbiota growth. Furthermore, the microbial metabolism of flavonoids may produce smaller molecules, which can be absorbed and transported to the distal organs. Moreover, flavonoid polymers such as proanthocyanidins, which are poorly absorbed in GIT, are metabolized by intestinal microbiota to more absorbable compounds like phenolic acids and Valero lactones, which can then produce systemic effects. The third possibility can be the biotransformation of the flavonoids in the intestine by the epithelial cells. The resultant conjugates can be transported into the blood or secreted back into the lumen; for example, EC sulfated by intestinal epithelial cells is secreted back to the lumen, which may undergo further metabolism or exert its local systemic effects. Hence, the initial metabolism of flavonoids is quite significant because it can modulate flavonoid absorption and may affect biological activity due to the conversion of the parent compound to its metabolites, which may be more or less effective. In conclusion, flavonoids and their metabolites can exert both local and systemic effects (Figure 1).

Classification and sources of flavonoids

Flavonoids are a collection of phenolic compounds which possess phenyl benzo (γ) pyrone-derived structure comprising of two benzene rings (A) and (B) joined through pyran rings. Based on the absence or presence of a carbonyl group (C = O) at position 4, with a double bond linkage at positions 2 and 3, or rather a hydroxyl group (-OH) attachment at position 3, they are generally subdivided into flavones, isoflavones, flavanones, anthocyanins, flavonols, and others (Figure 2) (Wang, Li, and Bi 2018).

According to the latest reports from the National Health and Nutrition Examination Survey (NHANES), the average intake of flavonoids in US adults is around 200–250 mg per day, about 80% (flavan-3-ols), over 8% (flavonols), with 6% (flavanones), about 5% (anthocyanidins), and almost ≤1% being (isoflavones and flavones) (Kim, Vance, and Chun 2016). The primary food sources of flavonoids are red wine, citrus, citrus juices, apples, berries, tea, and vegetables. Individualized flavonoid intake may fluctuate extensively depending upon whether tea, soy items, red wine, or commonly grown food such as vegetables and fruits are

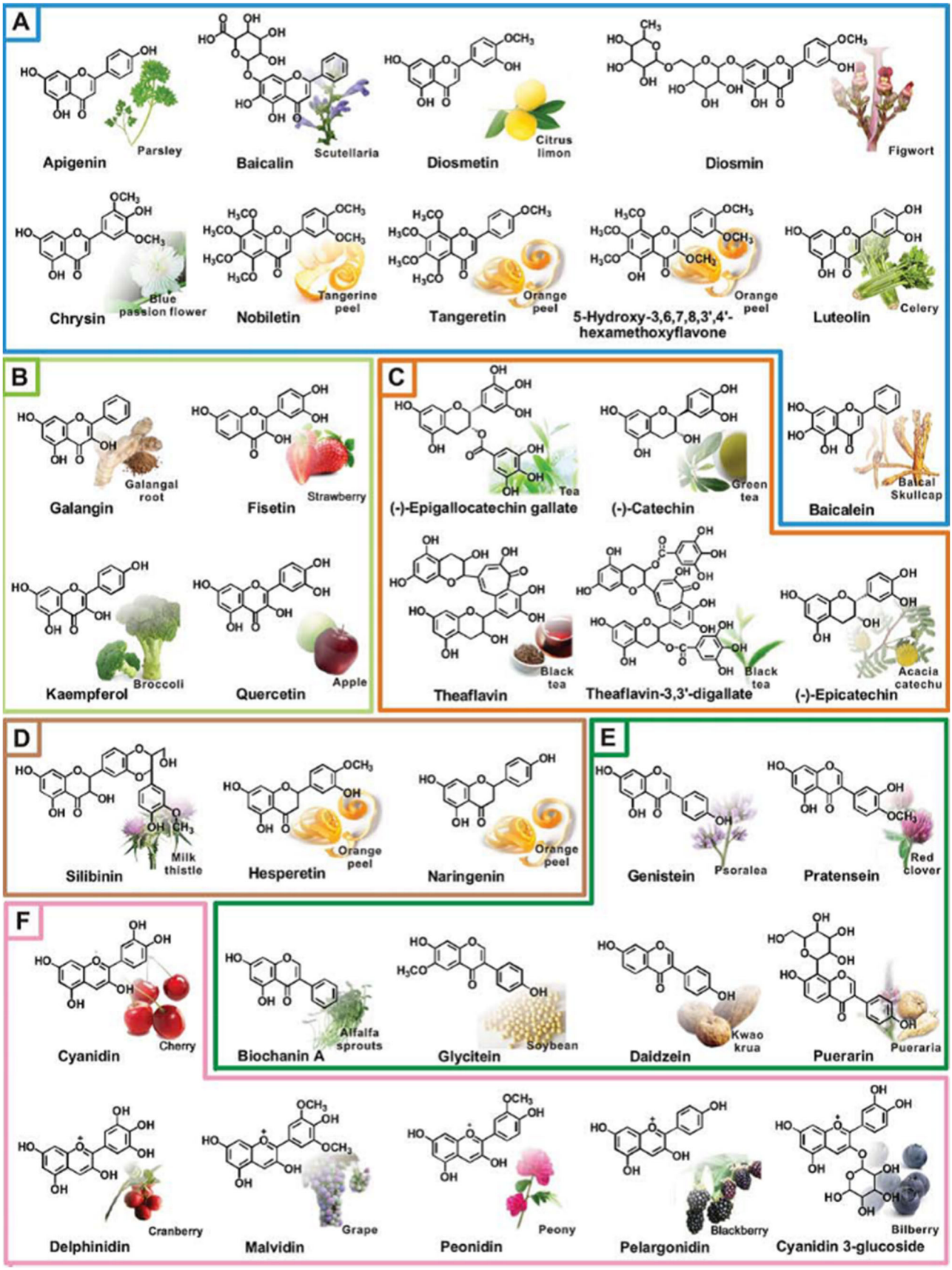

Figure 2. Representative flavonoids and their dietary sources. (A) Flavones, (B) Flavonols, (C) Flavanols, (D) Flavanones, (E) Isoflavones, and (F) Anthocyanidins. Reproduced from (Pan, Lai, and Ho 2010) with permission from The Royal Society of Chemistry.

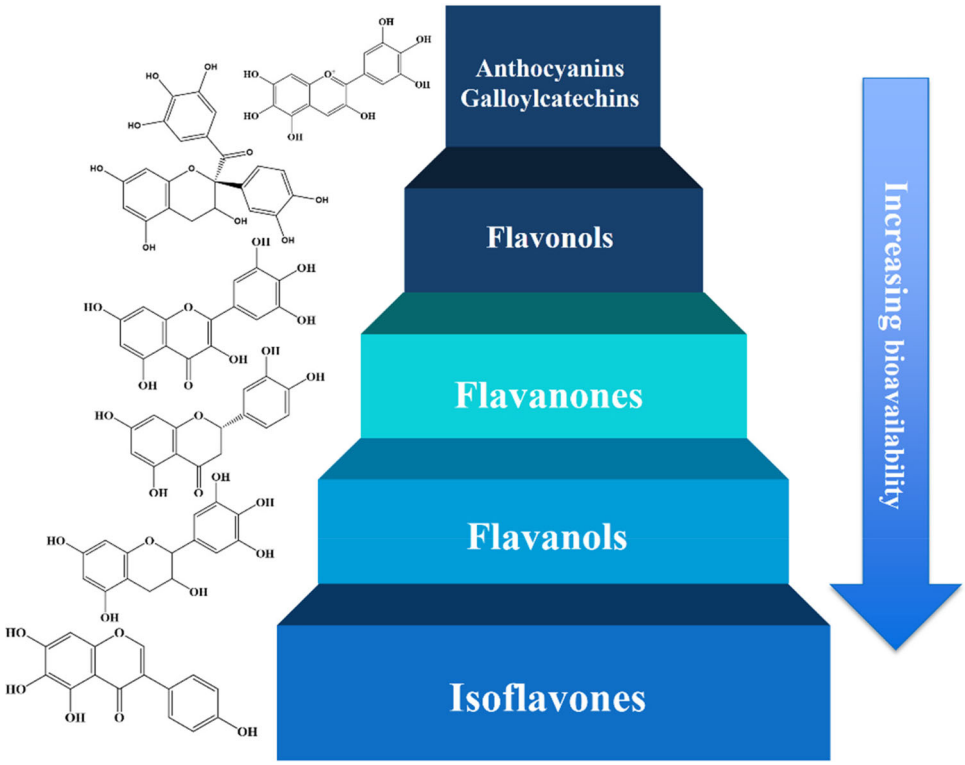

Figure 3. Variation in bioavailability with changes in the structure of flavonoids (Manach et al. 2005).

consumed. Moreover, various factors may influence the flavonoid content among these foods, Such as agricultural approaches, ripening techniques, storage, environmental conditions, and food processing (Thakur et al. 2020).

Flavonoids structure and bioavailability

Flavonoid's structure for quite some time has been viewed as an essential decisive criterion for bioavailability. Figure 3 outlines the results of a much-cited review, including 97 bioavailability reports concerning the bioavailability of flavonoids and presents a qualitative overview of the absorption of flavonoids in the GI tracts (Gonzales et al. 2015). Although, because of the more considerable structural variation in each group, it is hard to sum up, the absorption capability of flavonoids just based on their respective groups. For example, low oral bioavailability of flavonoids has been associated with the presence of free hydroxyl groups, which results in very rapid conjugation by glucuronidation and sulfation. Therefore, methylation is used to cap all free hydroxyl groups in order to eliminate conjugation as the primary metabolic pathway, which lead to improvements in metabolic stability and it has been observed that the methylated flavones are metabolically much more stable than the unmethylated analogues. Besides, the degree of glycosylation and the linked sugar type has been found to influence flavonoids bioavailability in comparison to their aglycone counterparts. Such as cellular models (Caco-2 cells) revealed that hydrophobic flavonoids are better absorbed, because of their higher permeation over the phospholipid bilayer of the cell membrane. In contrast, flavonoid glycosides are poorly absorbed through the intestinal cellular models because of the presence of sugar moieties, which increase hydrophilicity, resulting in decreased membrane permeability. However, in contrast to these in vitro results, animal and human studies revealed that certain flavonoid glucosides are more efficiently absorbed than their aglycone counterparts. For example, after administering quercetin-3-O-glucoside to pigs and rats, more significant amount of quercetin metabolites were observed in plasma compared to quercetin-3-O-glucorhamnoside (rutin), which appeared after three hours of administration. These lately observed peaks in plasma were ascribed to rutin deglycosylation by duodenal microbes and the absence of rhamnosidases within epithelium (Reinboth et al. 2010).

Contrary to O-glycosides, the C-glycosides exhibit more resistance to hydrolysis. The pharmacokinetics of vicein-2 (C-glycoside) has demonstrated a generally stable metabolic process (Wang, Li, and Bi 2018). Meanwhile, relative absorption of apigenin and associated glycosides, resulted in unchanged form of apigenin 8-C-glucoside-2-Oxyloside, while significant metabolites of apigenin/O-glycosides are associated aglycone along with glucuronides in portal bloodstream, has additionally approved the metabolic stability of C-glycosides (Buqui et al. 2015). Indeed, these studies have left space for detailed investigations with causal SAR about glycoside absorption.

Mechanism of flavonoids absorption

Following oral administration, flavonoids should be able to pass through the adherent intestinal mucus layer before their absorption. However, the effect of this mucus barrier on the intestinal absorption of flavonoids and its glycosides is not well explored. Therefore, it has been hypothesized that the

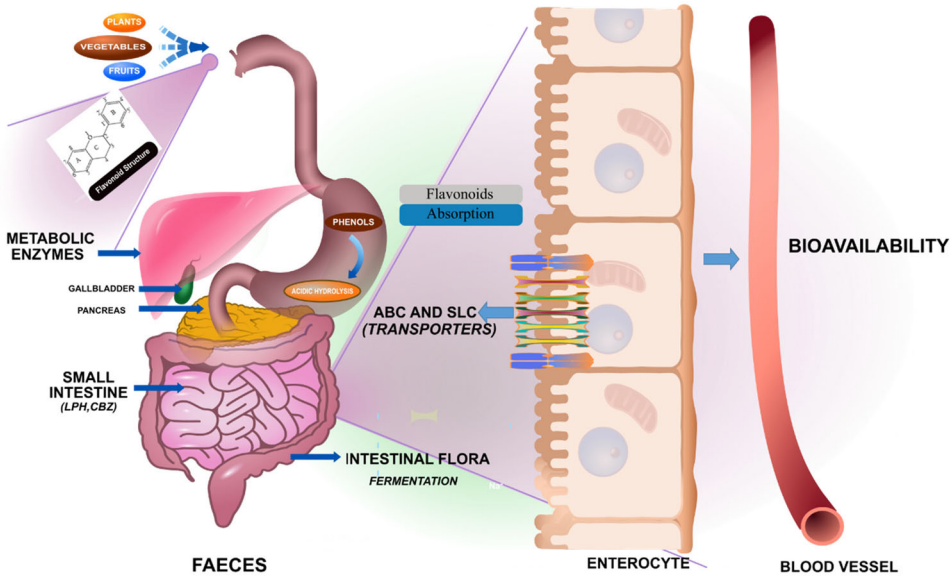

Figure 4. Routes of absorption and metabolism of Flavonoids in Humans.

hydrophobic nature of flavonoid aglycones may limits its penetration, as a result, are inaccessible to the cells. Though, flavonoid glycosides may penetrate through the mucus layer and then deglycosylated at cell surface, as aglycones interacts more strongly with food and digestive enzymes, resulting in its absorption. And the initial step for deglycosylation might be the deglycosylation via active uptake by (SGLT1) transporter. Followed by hydrolysis via enzymes like lactase phlorizin hydrolase (LPH) and deglycosylation by cytosolic β-glycosidase, and then released aglycones are passively diffused across epithelia (Day et al. 2000). However, rhamnose linked flavonoids are only hydrolyzed by α-rhamnosidases in colon, secreted by colonic microbiota (Figure 4). It is worth mentioning that deglycosylation pattern may rely upon the nature of aglycone and linked sugar type.

The absorption pattern of flavonoid glycosides has been extensively studied and attributed to the absorption enhancement effect of SGLT over glucosides. But, SGLT may not be the only clarification for better absorption, considering the highly hydrophilic nature of glucosides, the diffusion to LPH arrayed brush border via unstirred water layer becomes easier (Wang, Li, and Bi 2018). Moreover, internalization in polar-nonpolar membrane-interface, mainly accomplished by electrostatic and lipophilic links with phospholipids, can be acquired by assessing structural characteristics of flavonoids, to predict the bioavailability. Therefore, aglycones exhibit faster absorption and higher bioavailability than glycosides due to superior membrane interactions, although most flavonoids exist in glycosidic form.

As mentioned above, aglycones interact strongly with food and digestive enzymes than aglycones counterparts. Hence, glucosides exhibit greater in vivo absorption than in vitro cell-based models such as Caco-2 cells, which are unable to form a mucus layer. Nowadays, cell models include co-culture of enterocytes with mucus-forming cells and are progressively being utilized to tackle this frailty, even though the data is rare. A hypothetical model to predict the absorption of flavonoids based on the data from literature is shown in (Figure 5).

Factors affecting bioavailability of flavonoids

The primary drug absorption process happens in the small intestine. Intestinal flora, transporters, metabolic enzymes, food matrix and plasma protein binding affects the absorption and distribution of the drug and nutrients. Factors responsible for the low and inconsistent bioavailability of flavonoids, are discussed in detail (Table 1).

Intestinal flora

The small intestine is a perplex organ with movements, intestinal flora, and mucus. Microbiotic flora is a fundamental component of the gut. According to modern microecology, a variety of bacteria present in the human gastrointestinal microbiota has an essential impact in absorption yet also in the formation of enzymes, nutrients, and in controlling the immune system (Billat et al. 2017). The activity and diversity of colonic bacteria partly depend on an individual's dietary habits and will determine the nature of metabolites produced from ingested flavonoids. The metabolic products and bioavailability of flavonoids are highly influenced by the composition of the colonic microbiota (van Duynhoven et al. 2011). Mucus is a vital element of the GI tract, providing a physicomechanical hindrance, yet additionally a place for microbes.

Usually, a tiny portion (20%) of the orally administered polyphenol is absorbed within the small intestine and enter into the systemic circulation. Moreover, the majority dose is transported to the colon due to the poor intestinal absorption of phenolics. Therefore, potential benefits of nutritional

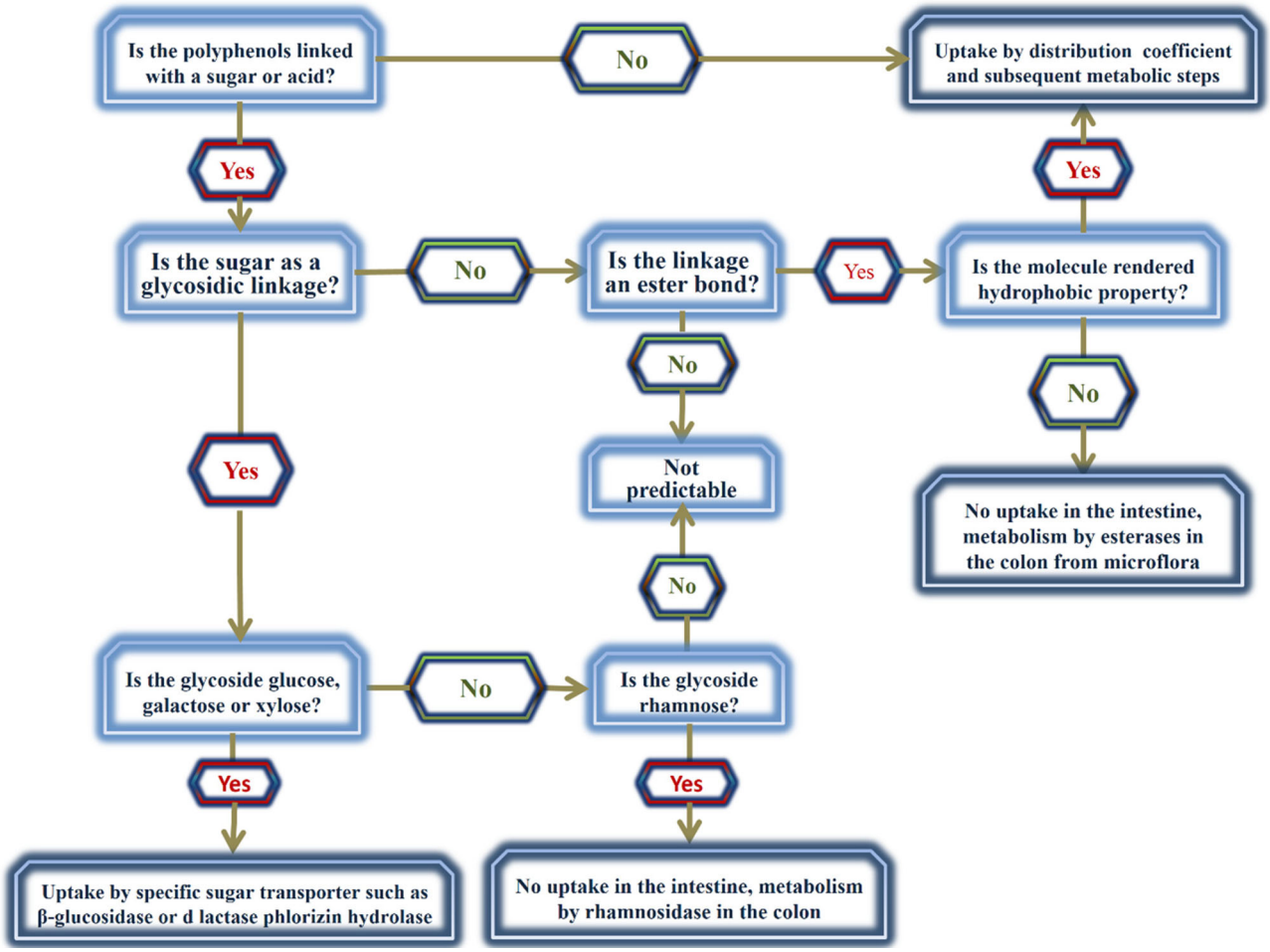

Figure 5. Hypothetical model based on literature to predict the absorption of flavonoids in humans. Adapted from (Chen, Cao, et al. 2018) with permission from B. V Elsevier (Copyright © 2018).

phenolics may be achieved in the GI tract, and especially at the large intestine site due to prolonged exposure time and its resident microbiota. The unabsorbed phenolics which enters the colon are metabolized by gut microbiota into various smaller parts by deglycosylation, dehydroxylation, demethylation, and ring fission, etc. into simpler metabolites which are then absorbed or excreted, e.g., simpler flavonoids (out of polymerized flavonoids), phenolic acids, and γ-valerolactones, etc. (Wan, Co, and El-Nezami 2021).

For instance, some primary microbial metabolites produced from flavan-3-ols are ferulic acid, vanillic acid, isoferulic acid, caffeic acid, m-coumaric acid, hippuric acid, p-coumaric acid, and gallic acid (Bittner et al. 2014). Colonic microbes mediated chemical transformation of flavonoids may increase their bioactivities, such as isoflavones derived from soy. Monomers are directly metabolized into smaller phenolics, whereas larger compounds are initially converted into smaller polymerized (DP) compounds, although colonic bacteria may limit the absorption of aglycone flavonoids in the colon by removing sugar moieties and rapid degradation.

Membrane transporters

The low bioavailability and subsequent low level of dietary flavonoids in plasma create doubts over the mechanisms through which they achieve appropriate intracellular levels in the targeted tissues. Because flavonoids are generally hydrophilic (low log P) with lower molecular weight, the transportation of flavonoids across the cell membrane should occur by specialized transmembrane transporters, instead of simple diffusion across the lipid bilayer of the membrane. Thus, the transporters should be considered as significant factors in limiting the functional activity of flavonoids on cellular and organ level in the cardiac, renal, hepatic, and CNS, and various other tissues (Jiang 2014).

Usually, a flavonoid molecule seems to be a substrate of efflux transporters that further restricts its bioavailability. The in situ single-pass intestinal perfusion study demonstrated that absorption of flavone scutellarein and its conjugate (scutellarin) formation was enhanced in the rat jejunum after the perfusion of various inhibitors such as verapamil (p-gp), reserpine (BCRP), and probenecid (MRP2). In vitro studies performed in Caco-2 cells established their involvement in scutellarein absorption (You et al. 2014). Experimental data on transport and absorption of rutin in Caco-2 cells also revealed that apical-basolateral transport improved after utilization of transporter inhibitors cyclosporine, verapamil, and MK157, which further confirmed the role of MRP2, P-gp, and MRP3 in effluxing rutin through the apical membrane. The permeability coefficients

Table 1. Relationship between the intestinal barrier and flavonoids.

Flavonoids	Structure	Pharmacological applications	Bioavail-ability (%)	Results	Remarks	References
Apigenin	Flavone	Anti-cancer, anti-viral, neuroprotective, anti-inflammatory, antibacterial anti-oxidant, reproductive endocrine regulation, hypoglycemic, prevent and treat cardiovascular diseases	3–5	Subjected to methylation, sulfation, and glucuronidation Transported by efflux transporters, i.e., multidrug resistance protein-1 (ABCB1, CD-243) and multidrug resistance-associated protein-2 (ABCC2 and CMOAT) Intestinal secretion of flavonoids in Gunn rats (lacking UGT1A) were higher than Wistar rats for apigenin	Poor bioavailability due to rapid metabolism in the intestine than in the liver through the involvement of UGTs	(Ali et al. 2017; Madunić et al. 2018)
Baicalein	Flavone	Antitumor, antiviral, anti-oxidant, antibacterial, protect heart and cerebrovascular neurons, analgesic, anti-inflammatory, hepatoprotective, prevent and treat diabetes	13.1–23.0	Dissolution of pure baicalein (6.88 %) and BaPC (20.84 %) at same interval Good fat solubility and hydrophobicity Baicalein is metabolized to baicalin Baicalein is challenging to be directly absorbed	Low solubility leads to poor bioavailability The intestinal flora extensively metabolizes baicalein	(Chen et al. 2017; Zhou et al. 2017)
Chrysin	Dihydroxyflavone	Neuroprotective, antidepressant, anti-epileptic, anti-amyloidogenic, antiatherogenic, anti-oxidant, anti-inflammatory, anticancer, antiviral, anti-allergic, antiestrogens, anti-anxiety, antihypertensive	0.003–0.02	Poor water solubility, significant presystemic elimination in enterocytes and hepatocytes MRP4 was identified as an exporter for chrysin	Limited bioavailability, MRP4 affects the absorption of chrysin	(Nabavi et al. 2015; Mani and Natesan 2018)
Hesperidin	Dihydroflavone	Anticancer, anti-oxidant, anti-inflammatory, antibacterial, antiviral, anti-allergic, regulate immunity, cardioprotective, radioprotective, reduce cholesterol, anti-depressant, hypoglycemic	$<$25%	Hesperidin is poorly soluble in water, Hesperidin is absorbed throughout the small intestine and has a long absorption window The absorption mechanism of hesperidin is passive diffusion	Solubility restricts its bioavailability Hesperidin has a long retention time in the intestine	(Zhankun and Fang 2011; Ruge et al. 2015)
Luteolin	Flavone	Anti-inflammatory, antibacterial, anti-drug resistance, anti-inflammatory, anti-oxidant, antiviral, anticancer, hypolipidemic, anti-fibrosis, analgesic, hypoglycemic, immunomodulatory, and neuroprotective	4.10–26	Luteolin can produce six glucuronic acid metabolites in an in vitro glucuronidation metabolic system The inhibition of UGT1A9 and HLM metabolism by carvacrol was concentration-dependent Ko143 can significantly reduce the efflux rate of luteolin metabolites and increase the accumulation of intracellular metabolites	Luteolin can be metabolized by UGT and the luteolin metabolite is a substrate for the efflux transporter BCRP	(Sarawek, Derendorf, and Butterweck 2008; Wu et al. 2015)
Liquiritigenin	Dihydroflavone	Anti-inflammatory, antiviral, antitumor, anti-allergic, anti-depressant, improve vascular endothelial cell proliferation and migration, anti-oxidant, inhibit lipid peroxidation, treat chronic hepatitis	5–16	The P_{eff} of Liquiritigenin in the duodenum, jejunum, and ileum were $(70.7 \pm 2.7) \times 10^{-6}$, $(101.1 \pm 4.7) \times 10^{-6}$ and $(73.1 \pm 2.4) \times 10^{-6}$ cm·s^{-1}, respectively 10 μM Liquiritigenin shows about 60% activation of CYP2D6	The intestinal absorption of Liquiritigenin is good Glycyrrhizin may not be an inhibitor	(Alrushaid et al. 2017; Huaxiang et al. 2019)
Fisetin	Flavonol	Anticancer, antidepressant, anti-oxidant, anti-inflammatory, neuroprotective, anticoagulant, and treat diabetic kidney damage	7.8–44.1	Low water solubility, extensive first-pass metabolism, P-gp-mediated efflux and enzymatic degradation in the GI tract	Poor oral absorption because P-gp affects the absorption of fisetin	(Jo et al. 2016; Kadari et al. 2017)
Galangin	Flavonol	Anti-tumor, anti-oxidant, anti-mutative, antiviral, antimicrobial, anti-inflammatory, anti-obesity, anti-	3.67–7.6	Significantly increased CYP1A1 expression in B(a)P-induced models, compared with control groups Pre and post-treatment by galangin	Galangin affects the expression of cytochrome P450 1A1 protein	(Devadoss, Ramar, and Chinnasamy 2018; Lu et al. 2019)

(*continued*)

Table 1. Continued.

Flavonoids	Structure	Pharmacological applications	Bioavail-ability (%)	Results	Remarks	References
		hypoxia, regulate smooth muscle contraction		significantly ($p < 0.05$) decreased the expression of CYP1A1 compared to B(a)P-induced model. No significant variation in Ka and P_{app} of galangin between the ileum and the control group after P-gp inhibition ($p > 0.05$)	P-gp has little effect on intestinal absorption of galangin	
Hyperoside	Flavonol	Anti-thrombotic, antibacterial, effective in cardiovascular diseases, antitumor, anti-aging, anti-depressant, anti-inflammatory, anti-oxidant, hepatoprotective, immunomodulatory, protect against brain ischemia	26.0	Hyperoside inhibited the IC_{50} of five P450 isoenzymes by $>10\ \mu$mol/L Metabolite:>9 The P-gp inhibitor can promote hyperoside absorption	Hyperoside is extensively metabolized in the body P-gp attenuates the absorption of hyperoside	(Guo et al. 2015; Shen et al. 2016)
Icariin	Flavonol	Osteoprotective, neuroprotective, cardio-protective, anti-cancer, anti-inflammatory, immunoprotective, improve reproductive system, anti-depressant, and hypouricemic	12	Interact with BCRP and MRP2 Extensively hydrolyzed in the small intestine and releases one or more sugar moieties Increased solubility and/or P-gp inhibition by β-CD and HP-β-CD	Poor solubility, Poor-membrane permeability, Poor oral absorption and P-gp inhibition	(Li et al. 2013; Niu et al. 2015)
Isorhamnetin	Flavonol	Anticancer, hypoglycemic, anti-atherosclerosis, anti-ischemic, lower blood pressure, anti-oxidant, antiviral, anti-inflammatory, and inhibit myocardial fibrosis	2.64	50 μmol/L isorhamnetin inhibited CYP2E1 and CYP1A2	Isorhamnetin may cause changes in the expression of CYP2E1 and CYP1A2 substrate drugs in the body	(Li et al. 2016; Rongjia et al. 2017)
Kaempferol	Flavonol	Anti-inflammatory, anti-cancer, inhibit thrombosis and platelet activation, anti-oxidant, protects cardiomyocytes, neuro-protective, hepatoprotective, anxiolytic effects	2-20	low liposolubility and poor water solubility, Kaempferol has a large particle size Rat cytochrome P450 1A1 catalyzes the oxidative metabolism of kaempferol kaempferol is probably a substrate and inhibitor of P-glycoprotein (P-gp) and BCRP	Poor oral absorption, CYP450, P-gp, and BCRP affects the absorption of kaempferol	(Zhang et al. 2015; S Qian et al. 2016; Zabela et al. 2016)
Myricetin	Flavonol	Anti-oxidant, anti-inflammatory, antitumor, hypoglycemic, analgesia, hepatoprotective, antihypertensive, acid resistant, anti-neurodegenertive, anti-allergic, antimicrobial	<10	Poor stability and aqueous solubility of Myricetin, The P-gp inhibitor verapamil promotes the absorption of myricetin	Poor oral absorption, Myricetin is the substrate of P-gp	(Caifu et al. 2011; M. Liu et al. 2016)
Morin hydrate	Flavonol	Anti-inflammatory, anticancer, anti-oxidant, antiarthritic, antifertility	N/A	Low aqueous solubility, Orally taken morin (15 mg per kg) significantly enhanced AUC (45.8%), Cmax (32.0%) and absolute bioavailability (35.9%) of orally delivered etoposide compared to control Morin has comparatively less permeability potency through the intestinal membrane, (MRAP-1) activity in the gut	Poor oral absorption and Limited bioavailability, Morin inhibits CYP isoenzymes and P-gp in the gut	(Li, Yun, and Choi 2007; Zhang et al. 2018)
Quercetin	Flavonol	Anti-carcinogenic, anti-inflammatory, anti-viral, anti-oxidant, neuroprotective, hepatoprotective, cardioprotective,	16–27.5	Poor solubility of quercetin, UGTs metabolize quercetin, Intestinal flora has a ring-opening	Low oral utilization, high metabolic rate,	(Costa et al. 2016; Kaşıkcı and

		renal protection, bone and joint protection, and ocular protection		decomposition effect on quercetin, Que shows weak inhibition of intestinal OATP2B1 and hepatic OATP1B2 protein expression, High-dose quercetin intake resulted in a significant reduction in intestinal and hepatoproteins expression as well as P-gp	Affects OATPs and P-gp	Bağdatlı oğlu 2016)
Rutin	Flavonol	Antioxidant, UV protection, protect gastric mucosa, anti-osteoporosis, enhance immunity, anti-aging, anti-cancer, hypoglycemic, antiviral, bacteriostatic, anti-inflammatory, analgesic, dilate blood vessels, neuroprotective, cardioprotective,	8.62	The primary metabolites of rutin are quercetin, Metabolic products:22 Mistletoe metabolized by UGT	Rutin can be metabolized by intestinal flora. Rutin is also affected by UGT	(Q. Wang et al. 2017; Ravi et al. 2018)
Silymarin	dihydroflavonol	Regulate liver function, protect pancreatic cells, antitumor, anti-oxidant, anti-inflammatory, anti-allergic, anti-diabetic, antiplatelet aggregation, hypolipidemic, anti-tuberculosis, anti-radiation, and protect brain tissue	0.95–40	Poor solubility in water and most organic solvents Silymarin inhibits CYP3A4, CYP2E1, CYP2D6, CYP2C19, CYP1A2, CYP2A6 and other metabolic enzyme activities in vitro Reduce the activity of UGT1A1/UGT1A9 by 65% and 100%, respectively, in vitro. Inhibits P-gp-mediated efflux of substrates in cells	Poor oral absorption, Silymarin effects CYP450 and UGT, P-gp affects the oral absorption of silymarin	(Sonali et al. 2010; Qinquan et al. 2015; Jianqiao, Ying, and Yanhua 2017)
Taxifolin	Flavonol	Anti-inflammatory, anti-oxidant, antiviral, antidiabetic, prevent alzheimer's disease, antitumor, antimicrobial, immunomodulatory neuroprotection, hepatoprotective, cardioprotective	0.17–0.49	Poor water solubility, Low dissolution rate in aqueous gastrointestinal fluid solution	Poor oral absorption	(C.-J. Yang et al. 2016; P. Yang et al. 2016)
Epigallocatechin gallate	Flavanol	Anticancer, anti-oxidant, antihypertensive, anti-mutative, cardioprotective, conditioning of endocrine, prevent diabetic nephropathy, hypoglycemic, anti-atherosclerotic, antibacterial, anti-viral, and CNS protective	12.4–26.5	EGCG inhibited CYP1A2 and CYP3A4 significantly, CYP2C9 slightly, but had no significant inhibitory effect on CYP2D6 Inhibits the activity of UGT1A1 EGCG is a substrate for many UGTs EGCG inhibits a variety of drug transporters in vitro, including OCT1, OCT2, MATE1, MATE-K, OATP1B1, OATP1B3, and P-gp	EGCG has different degrees of inhibition and regulation of both phase I and II metabolic enzymes EGCG regulates multiple drug transporters	(Gan et al. 2018; Qiuxin et al. 2019)
Epicatechin	Flavanol	Lipid and B.P-lowering capacity, anti-oxidant, bacteriostatic, anticancer, anti-inflammatory, increase mitochondria in the body, neuroprotective, cardioprotective, and hypoglycemic	5–39	22 ± 4 mg in 50 mg EC is directly released into the large intestine, Under eating conditions, the AUC and Cmax of EC increased to some extent ($p < 0.05$)	EC can be widely metabolized in the intestinal flora Food has a specific effect on the metabolism and absorption of EC	(Lin and Yumei 2017; Bernatova 2018)
Eriodictyol	Flavanone	Anti-oxidant, and anticancer	N/A	Relative bioavailability of eriodictyol was improved upto 216.84% by coadministering with glycyrrhetinic acid (GA), Low-level expression of cytochrome P450 monooxygenase	UGT affects Eriodictyol bioavailability	(Z. Wang et al. 2017)
Farrerol	Flavanone		37.3–42.2	About 70% of oral farrerol is absorbed but slowly,		(Piao et al. 2017; Wang et al. 2019)

(*continued*)

Table 1. Continued.

Flavonoids	Structure	Pharmacological applications	Bioavail-ability (%)	Results	Remarks	References
		Neuroprotective, inhibit angiogenesis, dilate blood vessels, antibacterial, anti-oxidatnt, and hepatoprotective		Farrerol is rapidly transformed in the body	Low drug distribution after oral administration	
Naringenin	Flavanone	Anti-atherosclerotic, anti-oxidant, anti-inflammatory, antitumor, antiviral, antibacterial, anti-fat production, cardioprotective, anti-allergic, antiestrogens	5.8–10	low water-solubility, Low dissolution rate, Naringenin shows inhibition of P-gp-mediated extracellular flow of P-gp substrates	Poor oral absorption and Naringenin may affect the ADME of P-gp substrates	(E Orhan et al. 2015; Surampalli, Nanjwade, and Patil 2016; Salehi et al. 2019)
Biochanin A	Isoflavone	Anticancer, estrogen-like action, anti-inflammatory, neuroprotective, anti-alzheimer's disease, and anti-HIV, anti-osteoporosis, antibacterial, hypoglycemic, hypolipidemic, antiasthmatic, repair skin barrier function, and whitening	1.2–4.6	Poor solubility, high clearance, large apparent volume of distribution BCA inhibits CYP 3 A and P-gp	low oral bioavailability, BCA affects P-gp and CYP 3 A	(Taneja et al. 2013; Wu et al. 2017)
Daidzin	Isoflavone	Prevent early atherosclerosis, hypolipidemic, antitumor, and regulates lipid metabolism	40	Inhibit CYP2C9 enzyme activity	Low aqueous solubility, CYP2C9 may affect the absorption of daidzein	(Kopecna-Zapletalova et al. 2017)
Genistein	Isoflavone	Anticancer, prevent and treat osteoporosis, cardioprotective, improve immunity, anti-depressant, bacteriostatic, hypolipidemic	<20	Poor aqueous solubility, P-gp may also have an efflux effect on genistein Bidirectional transport in BCRP or MDR overexpressed MDCKII cells	Poor bioavailability, Genistein is a weak substrate of BCRP	(Yang et al. 2012; Wang et al. 2014)
puerarin	Isoflavone	Antipyretic, antibacterial, lower blood pressure, hypoglycemic, hypolipidemic, anti-oxidant, cardioprotective, and reduce intraocular pressure	3.75–6.40	Poorly water-soluble, Rapidly metabolized by phase I metabolizing enzyme cytochrome after oral administration due to the first-pass effect Puerarin is absorbed in the intestinal mucosa by active transport Self-concentration inhibition	Low bioavailability, Puerarin is challenging to be absorbed in the gastrointestinal tract	(Chuanlian et al. 2012; Liping et al. 2019)
Anthocyanidin	Anthocyanidin	Anti-oxidant, antimicrobial, anticancer, anti-inflammatory, cardioprotective, reduce the risk of diabetes and cognitive dysfunction, anti-obesity, cytoprotective, and neuroprotective	11–13.76	Anthocyanins undergo extensive first-pass metabolism, SGLT1 and GLUT2 mediates the absorption of Cy-3-G in Caco-2 cells	Limited Absorption, SGLT1 and GLUT2 may be limiting Cy-3-G bioavailability	(Fang 2014; Fernandes et al. 2015)
Isoliquiritigenin	Chalcone	Antitumor, anti-oxidant, anti-inflammatory, and cardioprotective	22.70–33.62	Isoliquiritigenin is not water-soluble and fat-soluble, Isoliquiritin shows Nrf2-mediated transactivation of GCLC, UGT1A1, and MRP2	Poor oral absorption, Isoliquiritigenin affects UGT1A1 and MRP2	(Qiao et al. 2014; Gong et al. 2015)
Phloretin	Chalcone	Bacteriostatic, anti-oxidant, anticancer, anti-inflammatory, cardioprotective, cytoprotective, hypoglycemic, immunomodulatory, reduce melanin	0.49	Very poor water solubility, Strong inhibitory effect on P-gp, inhibits side effects of other GLUTs such as GLUT1 and GLUT2	Low oral bioavailability, P-gp affects the absorption of phloretin	(Pengfei 2012; Jung, Jang, and Park 2014; Barberis et al. 2017)

of BCRP substrates such as Isoflavones, daidzein, genistein, and their microbial metabolites dihydrodaidzein and dihydrogenistein were increased by using estrone-3-sulfate (BCRP inhibitor) in Caco-2 cell line (Čvorović et al. 2018).

Nevertheless, daidzein is also thought to be transported by P-gp and MRPs because verapamil and MK571 enhanced its transport from the apical-to-basolateral side, respectively. Several studies have shown that a significant quantity of absorbed catechin was effluxed back into the lumen in the unconjugated form (-)-epicatechin or conjugated with sulfate by biliary excretion processes. Jia et al. have demonstrated the effect of efflux transporters in reducing the bioavailability of Biochanin A (Jia et al. 2004).

Recently, the interactions of flavan-3ols such as (EC, ECG, EGC, and EGCG) with a section of the OATP/SLCO family were demonstrated. This study indicated that OATP1A2, which is available at the apical side of enterocytes, may influence the absorption of ECG and EGCG over the intestinal lumen (Roth, Timmermann, and Hagenbuch 2011). Another study also confirmed the involvement of OATs and OATPs in the intake of quercetin conjugates (sulfates and glucuronades) in HEK293 and HepG2 cell lines (Wong et al. 2012). In contrast, the possible mechanism for sulfates uptake was carrier-mediated, while glucuronides entered the cell via passive diffusion. OAT and OATPs inhibitors substantially decreased the absorption of quercetin-3′-O-sulfate in HEPG2. When HEK293 cells, having highly expressed OAT2, OAT4, and OATP4C1 were utilized, it was observed that quercetin-30-O-sulfate uptake was increased with the overexpression of OAT4 and OATP4C1. Moreover, the uptake of flavonoids was reduced by 40% after silencing OATP4C1 by siRNA in HepG2 cells (Čvorović et al. 2018).

Metabolic enzymes

The distinctive proof of metabolites of a potential drug candidate gives fundamental data on medication adequacy and its toxicological properties, which may lead to the age of new and improved medicinal structures. Flavonoids exhibit high bioactivity and low toxicity, which makes their therapeutic utilization more valuable (Vanzo et al. 2011). Poor absorption and extensive metabolism are associated with the lower plasma concentrations of flavonoids. Moreover, a large fluctuation is observed in their metabolism, for instance, methylation, sulfation, glucuronidation, and various conjugations, that additionally increases the diversity of chemical molecules which may serve as substrates of the transporters.

Bioactive flavonoids from traditional drugs undergo phase I and II metabolism in humans. Phase I metabolism via CYP mediated pathway plays a less prominent role in flavonoid absorption. The phase II enzymes (SULTs and UGTs) catalyze the Phase II metabolic reactions, which forms highly hydrophilic conjugated compounds e.g., glucuronides and sulfates, which can be easily excreted from the body. Failure or inadequate removal of these compounds will negatively impact the whole cellular metabolic process due to the prolonged exposure of the parent molecule. Because phase II metabolites accumulations favor the deconjugation reactions, which convert back the metabolite into parent molecules; as a result, reducing the whole metabolism (Hu, Wu, and Liu 2017).

The studies of Yang et al. have shown that a significant part of genistein was rapidly metabolized after oral administration by phase II conjugation reactions into glucuronide and sulfate metabolites in the liver and intestinal tissues causing reduced systemic concentrations of aglycones (Yang et al. 2012). The studies performed on flavonoids such as apigenin and quercetin have shown that intestinal and microbial glycosidases effectively hydrolyze glycosides, which are then further subjected to intestinal presystemic glucoronidation by phase II enzymes. Thus, presystemic activity is an important initial step before enteral and entero-hepatic recycling, which involves both apigenin and quercitin. Kim et al. have unequivocally shown the CYP3A inhibitory capacity of puerarin (Kim et al. 2014).

Food matrix

The food macronutrients also affect the bioavailability of co-ingested flavonoids. The physicochemical properties of flavonoids influence the binding affinity and possible (non-) covalent linkages with food proteins, fats, and carbohydrates (Gonzales et al. 2015). Milk proteins may decrease the absorption of polyphenols from black tea or cocoa. The flavonoids bound to milk proteins were found to weaken the anti-oxidant activity of flavonoid in vitro, and milk utilization has been proven to brusque the vascular advantages of tea flavonoids in healthy human volunteers (Xiao et al. 2011). Many high-carb foods may enhance the deglycosylation and uptake of flavonoids by stimulating GI motility, mucosal blood supply, and colonic fermentation. Alternately, dietary flavonoids also interfere with the digestion and absorption of carbohydrates (Lorenz et al. 2007).

Plasma proteins binding

Bioavailability of flavonoids might have an inverse relationship to plasma proteins binding affinity. Thus higher plasma protein binding (lower bioavailability) has been associated with their structural characteristics, e.g., gallolylation and methylation (Xiao and Kai 2012). Despite glycosylation, which reduces the plasma proteins binding, implying that aglycones may have a low bioavailability comparing to glycosylated flavonoids. Whereas glucuronidation facilitates the removal of flavonoids from the body. Due to lower plasma proteins binding affinity, glucuronides can quickly diffuse through and reaches the target tissues where deglucoronidation occurs (Dangles et al. 2001).

Strategies for bioavailability enhancement of flavonoids

To address the challenges of low oral bioavailability of flavonoids, various novel strategies are employed for enhancing its bioavailability, such as improving intestinal absorption

with absorption enhancer, changing absorption site from colon to the small intestine, increasing metabolic stability, structural transformation such as glycosylation and prodrugs, and pharmaceutical engineering, e.g., carrier complexation, nano-delivery systems, and microparticles, etc. These formulation techniques can significantly increase the oral bioavailability of flavonoids by improving dissolution rate, solubility, and permeability; by preventing degradation or metabolism in the GI tract; and/or deliver directly to intended physiological sites (Zhao, Yang, and Xie 2019). Some of these strategies are briefly discussed in this section.

Improvement of intestinal absorption

According to biopharmaceutical classification system (BCS), flavonoids aglycones and glycosides belong to BCS class II (low solubility and high permeability) and class IV (low solubility and low permeability) respectively. However, permeability is not a major issue for these flavonoids because glycosides are actively deglycosylated in the brush border by β-glucosidases, forming aglycone (highly permeable), which can penetrate across the mucous layer, and diffuse through the cell membrane. Therefore, increasing solubility will enhance permeability and ultimately improve bioavailability (Németh et al. 2003; Kaur and Kaur 2014).

Absorption/permeation enhancers

Absorption enhancers are used to enhance the absorption of pharmacologically active compounds for increasing their bioavailability. Many absorption enhancers have been proved to increase the bioavailability of peptides and high molecular weight compounds such as surfactants, fatty acids, chelating agents, bile salts, chitosan, and cyclodextrins and their derivatives (Maher et al. 2019; Yamamoto et al. 2020). A non-ionic surfactant (cremophor EL) significantly improved the area under the curve (AUC $_{0-12\,h}$) of scutellarin in rats from (365 ± 28 ngh/mL to 473 ± 64 and 587 ± 42 ngh/mL), by inhibiting apical transporters and stimulating basolateral side transporters (Xiao et al. 2016). Similarly, the AUC of quercetin was enhanced by using apple pectin from $3.45 \pm 0.67\,\mu M$ to $5.84 \pm 1.60\,\mu M$ (Xie et al. 2014). The oral absorption of puerarin was increased (0.908 ± 0.16 mgh/L to 4.184 ± 1.72 mgh/L), using chitosan-modified microemulsions by reversely opening the intestinal tight junctions. This approach is beneficial for hydrophobic flavonoids to overcome intestinal absorption difficulty without compromising the structural and biological activity of flavonoids (Liao et al. 2015).

Altering site of absorption

Flavonoids generally pass from the small intestine to colon, where extensively metabolized to phenolic acids by intestinal bacteria. Therefore, changing the absorption site from large intestine to small intestine can dramatically improve the bioavailability. Dietary fats and biles can form micelles, which acts as a carrier of aglycones and helps in penetration through the mucus layer, whereas hydrophilic glycosides can easily pass through it. It was found that the rutinose attached at position 7 of ring A in hesperidin molecule, was a key determining factor of absorption because glycosides with rhamnose were poorly absorbed than hesperetin or glucoside of hesperetin. However, enzymatic conversion of hesperidin to hesperetin-7-glucoside with hesperinidase increased bioavailability of hesperetin and decreased the time to achieve maximum plasma levels in humans. The cleavage of rhamnose changed the site of absorption and resulted in improving bioavailability (Nielsen et al. 2006).

Structural transformation

Structural modification of bioactive compounds from natural sources has been proved to be advantageous over the parent molecule, like improved bioavailability and pharmacological response due to higher dissolution rate and stability. Flavonoids have many hydroxy groups that are mainly responsible for the antioxidant activity and can be easily transformed to O-glycosylated, O-methylated, O-acylated, and O-sulfated forms. Many flavonoids parent molecules have been successfully transformed using these approaches for enhancing bioavailability (Teng and Chen 2019).

Glycosylation

Glycosylation is the most promising tailoring approach used for synthesis and modification of various bioactive substances to modify the physicochemical properties of the molecules. Different biochemical and molecular techniques are used to glycosylate flavonoids aglycones such as chemical synthesis, microbial biotransformation, and enzymatic manipulation (Ji et al. 2020). Such as conversion of daidzein to daidzein-7-O-β-D-glucoside significantly improved the solubility which leads to improved bioavailability. The solubility of flavonoid derivatives depends on the nature of reacted substrates, linked sugar moiety, technique, and site of O-glycosylation (Rüfer et al. 2008). The aqueous solubility of flavonoids is directly proportional to the degree of glycosylation. In order to avoid loss of any biological activities in flavonoids glycosylation, the steric hindrance should be built to the glycosyl donor if one diastereoisomer (α or β) is required for modification and choose proper glycosylation method based on the chemical structure of every flavonoid components with reduced reaction steps. Also, some glycosylated flavonoids exhibit new biological characteristics, like anti-viral, anti-depression, and anti-obesity, which can be of significant importance to prevent or treat various other diseases. Hence, further screening of pharmacokinetic and pharmacodynamics properties can help to detect valuable flavonoids derivatives for application in other related disorders (Zhao, Yang, and Xie 2019).

Prodrugs approach

A prodrug is an inactive biological derivative of a pharmacologically active ingredient that shows the desired pharmacological response by chemical and/or enzymatic transformation to the active parent molecules. Prodrug

strategy has been mostly employed for increasing the stability, and solubility of drug substances by presenting polar groups, i.e., Amino acids, sulfuric acid, and polymers into the molecule, which increases its polarity and reduces the hydrophobic character (hydrophobicity) and increase its solubility or by increasing the lipophilicity by shielding the polarized ionizable groups, which increases the oral absorption (Dhaneshwar and Bhilare 2020). Although an optimal "lipophilic-hydrophilic balance" is important for better absorption. Prodrugs of flavonoids have been reported, such as acacetin prodrug was synthesized, which improved the solubility and performance in in vivo and ex vivo studies (H. Liu et al. 2016). Myricetin derived oncamex has shown better performance in preclinical models of breast cancer, which shows that the derivatives of the flavonoids can be tuned to get the desired improved response (Martínez-Pérez et al. 2016). Furthermore, Chen et al. developed a prodrug of 7,8-dihydroxyflavone by modifying the carbamate group of catechol ring, which resulted in higher absorption (Oral bioavailability increased from 4.6% to 10.5%) in 5XFAD mice(Chen et al. 2018). Moreover, prodrugs are susceptible to intestinal metabolism before being absorbed and are degraded, in order to avoid the prodrugs are enclosed in novel nanoparticles formulations such as Cao et al. encapsulated scutellarin in O/W emulsion which reduced the intestinal degradation (Cao et al. 2006).

Enhancing the metabolic stability

Flavonoids have many free hydroxyl groups and carbon atoms, which can be masked by methyl groups to prevent their conjugation and enhance their metabolic resistance, which ultimately increases bioavailability. Such as methylated flavones, 5,7-dimethoxyflavone, and 3′,4′-dimethoxyflavone showed higher metabolic stability than non-methylated form (3,5,7-trihydroxyflavone). Similarly, monomethylated forms of kaempferol (kaempferide) and genistein (biochanin A) affinity was increased 2–16 times to transport proteins (albumin and ovalbumin), resulting in higher transport due to the binding ability, which increases with increasing hydrophobicity (Thilakarathna and Rupasinghe 2013). Additionally, orally administered chrysin was undetectable at tissue levels, but its methylated form reached higher levels in rats (Walle et al. 2007). Mono and dimethylated form of flavones increased their pharmacological response against human bronchial BEAS-2B cells by inhibiting carcinogenic stimulation of CYP450 transcription, aromatase (targeting site in hormonal cancers) and other DNA binding enzymes (Ta and Walle 2007; Tsuji and Walle 2007). Similarly, Copmans et al. showed that methylated form of Naringenin (Naringenin M and DM) has a great potential to treat neurological disorders such as epilepsy, which become resistant to standard treatment (Copmans et al. 2018).

Influence of food matrix

Food supplements are useful to improve the bioavailability of orally administered flavonoids. Because food ingredients can modify the physicochemical properties of the surrounding environment, such as pH, concentration, and intermolecular forces, which then affects the bioavailability, but, its success depends on proper screening of various food ingredients with different bioactive flavonoids. Such as bioavailability of epigallocatechin was increased by supplementation of steamed rice because of the presence of binding of proline-rich proteins to epigallocatechin via tannase, thereby increasing bioavailability. Furthermore, carbohydrate rich food matrix has been thought to be the determining factor for intestinal absorption of the total flavonol. Such as flavonols consumption with maltitol reduced their absorption compared to ingestion with sucrose without altering catechol-O-methyltransferase function (Monobe et al. 2011; Rodriguez-Mateos et al. 2012). Furthermore, the influence of the food matrix was more eminent when the flavan-3-ols concentration was lower. Similarly, quercetin has shown higher bioavailability if ingested with food like quercetin enriched cereal bars and quercetin rich onions (Terao 2017; Lin et al. 2019). However, these food materials should be individually evaluated to estimate their interaction with bioactive flavonoids and simultaneously increasing in vitro and in vivo experiments to establish the relationship of bioavailability of flavonoids to various food contents.

Inclusion complexes

Inclusion complexes of flavonoids with cyclodextrin have been shown to increase solubility and bioavailability, such as HP-β-CD complexation with apigenin, baicalein, daidzein, silibinin, quercetin, myricetin, scutellarein naringenin, puerarin, fisetin, and methoxyflavones, etc. Similarly, α, β and γ cyclodextrins complexes have been reported, such as baicalin, dry extract of Silybummarianum (silibinin, isosilybin A, and B, taxifolin, silydianin, silychristin) and extract of Soyisoflavone (genistein, daidzein, glycitein), naringenin and rutin, etc. (dos Santos Lima et al. 2019). Moreover, the inclusion complexes of these flavonoids improve their solubility, which ultimately enhances the bioactivities of the flavonoids. Moreover, solid dispersion is also used to enhance the solubility of flavonoids, such as THF solid dispersions increased the solubility of chrysosplenol C solubility three times more than native THF (Ng et al. 2016).

Phospholipid complexation is another approach to enhance the bioavailability of flavonoids because the complexes form between drug and phospholipid through hydrogen bonds and electrostatic interactions, which can improve both solubility and permeability. Due to higher biocompatibility of phospholipid with physiological systems, solubility and permeability of various flavonoids have been enhanced such as TFH-phospholipid complexes increased the saturation solubility of QU, KA and IS from 3.07 μg/mL, 1.0 μg/mL, 1.07 μg/mL to 82.28 μg/mL, 24.21 μg/mL, 23. 52 μg/mL, which resulted in improvement in the oral bioavailability of 242%, 172%, and 223% in rats, respectively (Xie et al. 2014; Wang et al. 2015).

Nanotechnology-based formulations

Conventional carrier systems of flavonoids like tablets, powders, and capsules are unable to solve the inherent problem of poor solubility and erratic bioavailability and non-uniform bio-distribution in body fluids. To effectively overcome these barriers, a nanotechnology-based formulation approach has been employed, which has been proved to have higher bioavailability, mean residence time, and biodistribution over conventional formulations. The uptake of nanoparticles from the GI tract occurs in three proposed ways: (1) paracellular (2) intracellular and (3) lymphatic pathway (Khan et al. 2021). There are many types of nanoparticles formulations of flavonoids reported which includes polymeric nanoparticles, nanocrystals, co-crystals, lipid-based nanosystems such as liposome, niosomes, solid lipid nanoparticles, and hybrid nanoparticles, micelles and nanoemulsions, nanosuspension, self-nano emulsifying drug delivery systems, etc. Nanocrystals of rutin, lutein, apigenin, quercetin, hesperidin, hesperetin, baicalein, epicatechin, and other flavonoids have been formulated, which increased its solubility and resulted in higher bioavailability (Gujar and Wairkar 2020). Phytosomes and liposomes of quercetin have been formulated, which significantly increase its bioactivity. Mostly their bioactive properties are drastically improved by formulating as nanoparticles such as baicalein nanoparticles effectively inhibited the tumor growth of A549 cells (Davatgaran-Taghipour et al. 2017). Similarly, chrysin nanosuspension inhibited the proliferation of HepG2 cells (Li et al. 2015).

Conclusion and future prospectives

In summary, along with physicochemical properties of flavonoids, the intestinal flora, membrane transporters, food matrix, protein binding, and metabolic enzymes are vital components of the gastrointestinal environment in which the flavonoid is located, which together constitute the gastrointestinal network barrier and play an essential role in flavonoid absorption and its efficacy. Therefore, studying the pharmacokinetics of flavonoids with and/or without food, especially the study of the gastrointestinal absorption barrier network, is a fundamental and essential scientific issue that cannot be avoided in the actual process of development and optimization of dietary flavonoids as a medicine. One of the critical factors that have turned out to be essential in elucidating the frequently variable and low bioavailability of flavonoids and other medications is the presence of intestinal transporters, together with drug-metabolizing enzymes and intestinal flora, that play a significant role within the disposition of orally administered medications, toxins, supplements, and xenobiotics. Therefore, controlled, long-term clinical trials showing critical endpoints should be performed for establishing their dosage-regimen and determining adverse effects which can happen due to mutual impact with intestinal barrier, to provide better food and drug-safety for patients.

The outcomes of in-vitro, in-vivo, and human studies need to be considered before future research, which can help in successful clinical translation of flavonoids. Continuous progress in flavonoids research is fascinating, but high-quality research input is required, which provides detailed information about safety, efficacy, and toxicology – also addressing drug development problems like processing, developing, large scale manufacturing, and patents, which have resulted in failed clinical translations. Novel formulation strategies and routes of administration of flavonoids and in-depth analysis of the absorption mechanism of these systems need to be investigated according to their pharmacological applications.

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