

Review

Metabolism of Flavonoids and Implications for Their Biological Activities: An Updated Review

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Abstract

Background/Objectives: Flavonoids are a diverse group of dietary polyphenolic compounds associated with a range of important biological activities. However, their low systemic bioavailability and extensive metabolism raise questions about how they exert their purported benefits. **Methods:** A comprehensive survey of literature published over the past 10 years was conducted, focusing on human, animal, and in vitro studies addressing the metabolic fate of major flavonoid subclasses. **Results:** Original research articles ($n = 159$) were selected following predetermined inclusion criteria. Data from diverse experimental models—including intestinal and hepatic systems—demonstrate that flavonoids undergo substantial transformation by Phase I and Phase II enzymes, alongside extensive biotransformation by the gut microbiota. In this critical narrative review we summarize dietary sources, bioavailability patterns, metabolic pathways, and analytical strategies, emphasizing advances enabled by high-resolution mass spectrometry. Recent findings indicate that enterohepatic recirculation and the biological activities of circulating and tissue-associated metabolites contribute significantly to the observed health effects, despite limited levels of parent compounds. **Conclusions:** Flavonoids exhibit limited oral bioavailability and undergo complex metabolic processing, yet growing evidence indicates that their metabolites play key roles in mediating beneficial effects. Understanding these metabolic pathways is essential for interpreting epidemiological associations and designing more effective intervention studies.

Keywords: flavonoids; polyphenols; metabolism; bioavailability; gut microbiota; diet



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1. Introduction

Flavonoids are naturally occurring polyphenolic compounds exhibiting a wide range of important biological activities. Numerous epidemiological studies, beginning in the 1990s and continuing to the present, have shown that a higher intake of flavonoids from the human diet has been correlated with decreased risk of all-cause mortality [1,2], cardiovascular disease [3], type-2 diabetes [4], cancer [5,6], neurodegenerative diseases [7,8] and pulmonary diseases [9,10].

Despite the epidemiological evidence for their health benefits, the oral human bioavailability of flavonoids occurring in dietary sources mainly as glycosides is generally low, and they suffer extensive intestinal and liver metabolism. Consequently, low circulating levels of parent compounds are usually found, which has hindered understanding of how flavonoids exert their biological effects.

The epidemiological evidence strongly suggest that high flavonoid intake is associated with better health outcomes such as reduced risk of cancer and chronic diseases. However, there is a gap in our understanding since the evidence from epidemiological studies does not address the question of what molecular species are involved in the final effects of flavonoids. As discussed throughout this review, accumulating evidence demonstrates that flavonoids undergo extensive metabolism in the intestine, liver and gut, which result in low circulating levels of parent compounds. This apparent discrepancy between consistent epidemiological data supporting health benefits and limited systemic levels of flavonoids in vivo has been called by some authors the “Flavonoid Paradox” [11,12]. Due to their extensive metabolism and low bioavailability of parent compounds, flavonoid metabolites (particularly glucuronidated, sulfated, methylated, and microbiota-derived products) may represent the major circulating forms and may play a major role in the alleged biological actions of flavonoids. Understanding the biological fate of flavonoids in vivo is therefore central to understand their role in the prevention of disease.

A significant body of research has accumulated on flavonoid metabolism, and there is some evidence that metabolites can play an important role in mediating some of flavonoids' biological actions [13]. Although several excellent reviews have addressed flavonoid metabolism, many focused on specific flavonoid subclasses, individual metabolic pathways, gut microbiota, or the biological activities of flavonoid metabolites. The present review differs by providing an integrated synthesis of original research published over the last decade, emphasizing recent advances in absorption, pharmacokinetics, host and microbial metabolism, experimental models, and high-resolution analytical strategies, together with the implications of these metabolic transformations for flavonoid biological activity.

2. Materials and Methods

2.1. Data Collection Strategy

A literature search was conducted in the Web of Science® Core Collection using the term “flavonoid metabolism” on 5 November 2025. The search was limited to articles published within the previous 10 years. Additionally, a search was performed in PubMed on 5 January 2026, using the query [“metabolism of” AND “flavonoids”]. Only studies published within the last 10 years were considered. No additional filters or restrictions were applied in either database. A deliberately broad search strategy was adopted to maximize retrieval of potentially relevant studies, with specificity being achieved during the screening stage through predefined inclusion and exclusion criteria.

2.2. Inclusion and Exclusion Criteria

This review included original research articles investigating the pharmacokinetics of flavonoids, with a focus on absorption, distribution, and metabolism. Studies employing both in vivo and in vitro experimental models were considered, including but not limited to liver microsomes, hepatocytes, and heterologously expressed enzyme isoforms. Eligible studies examined flavonoids either as isolated compounds or within complex matrices such as plant extracts or propolis. Studies addressing intestinal metabolism of flavonoids were also included.

The following exclusion criteria were applied: review articles; computational or in silico studies; investigations of flavonoid roles in plant secondary metabolism; studies on the effects of flavonoids on xenobiotic or endogenous human metabolism; general pharmacokinetic studies of plant extracts in which flavonoids were minor constituents; in vitro biotransformation studies involving isolated microorganisms or fungi; studies focusing on phenolic compounds other than flavonoids (e.g., phenylethanoids); dietary supplementation and food processing studies; research centered exclusively on the pharmacological

activity of flavonoid metabolites outside the context of flavonoid disposition; studies with focus on formulation to enhance flavonoid bioavailability; method development and validation studies; and conference abstracts.

2.3. Screening Procedure

All retrieved records were initially screened based on their titles. When eligibility was uncertain, abstracts were also evaluated. After removal of duplicate records, full texts of potentially relevant articles were obtained. Final inclusion was determined through comprehensive assessment of the full-text articles (Figure 1). Since the present work was designed as a critical narrative review and retrieved papers represent a heterogeneous body of work comprising *vitro* enzyme assays, cell culture studies, animal experiments, pharmacokinetic investigations, and metabolite identification studies, a formal quality assessment and risk-of-bias evaluation were not formally performed. This was because there is no validated quality assessment tool covering such broad and diverse experimental models. Screening was mainly driven by the predefined inclusion and exclusion criteria, and the experimental results were critically interpreted based on the models employed and their inherent limitations.

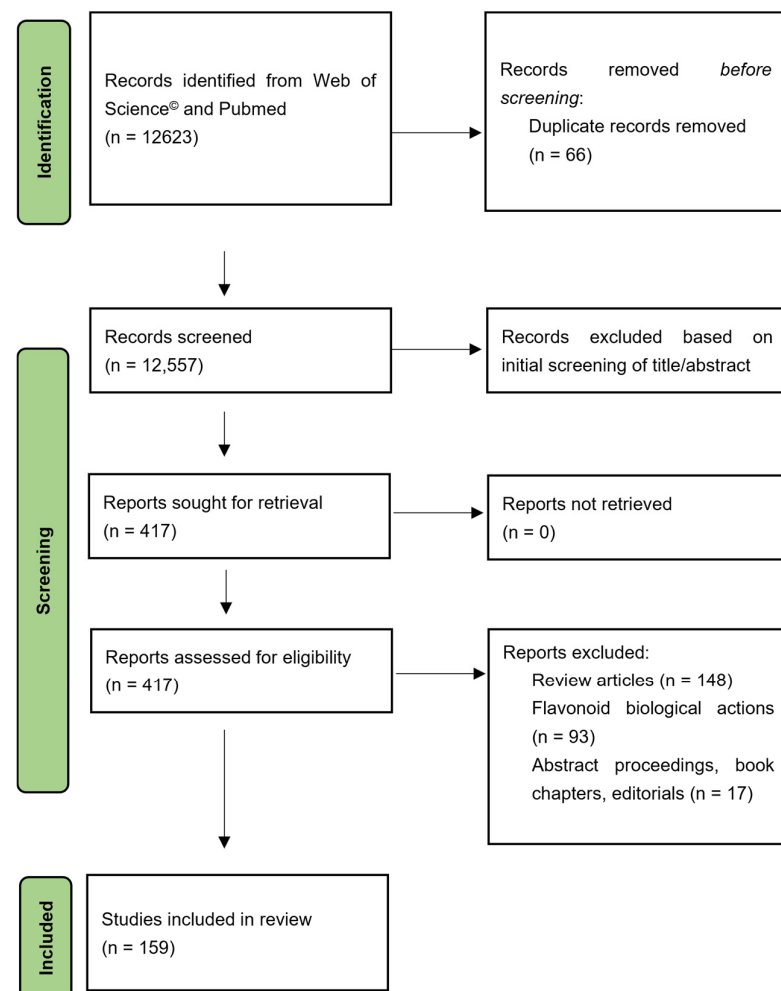


Figure 1. Flow diagram of literature search and study selection according to PRISMA guidelines.

3. Results and Discussion

3.1. Food Sources and Human Intake

3.1.1. Food Sources and Classification of Flavonoids

Flavonoids are phenolic structures, biosynthesized especially by plants through secondary metabolism and widely distributed in fruits, roots, stems, flowers, leaves, and seeds. They have attracted considerable attention due to their broad biological activities, including antioxidant, anti-inflammatory, antimutagenic, and enzyme-modulating properties, which contribute to health promotion and the prevention of chronic diseases. Consequently, flavonoids are extensively used in pharmaceuticals, cosmetics, and nutraceuticals [14–16].

Flavonoids share a common C6–C3–C6 backbone composed of two aromatic rings (A and B) linked by a three-carbon bridge, often forming a heterocyclic C ring (Figure 2). There are more than 8000 flavonoids identified in plants [17]. Their structural diversity arises from variations in the oxidation and substitution patterns of these rings. Flavonoid biosynthesis begins with the formation of chalcones by chalcone synthase, followed by enzymatic modifications that generate the different flavonoid classes and their glycosides.

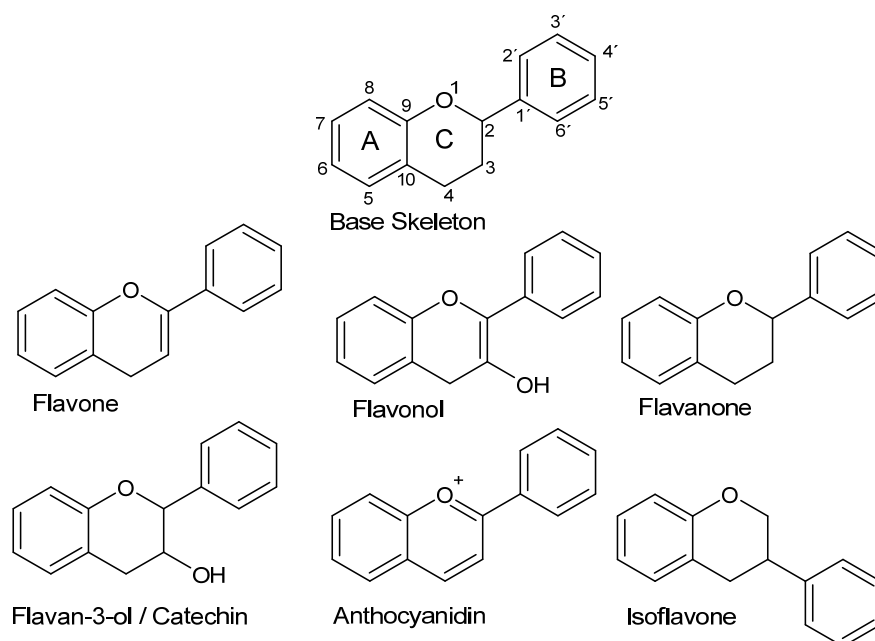


Figure 2. Basic flavonoid skeletons of the main classes of flavonoids found in foods.

The main dietary flavonoid classes are flavones (such as apigenin and luteolin), flavonols (e.g., quercetin and kaempferol), flavanones (such as naringin and hesperidin), isoflavonoids (such as daidzein, genistein and glycitein), flavanols or catechins (such as epicatechin), and anthocyanidins (e.g., delphinidin and cyanidin) (Figures 2 and 3) [15–20].

The main sources of flavonoids for human nutrition are of plant origin. Although the concentration varies drastically between species and parts of the plant, there are food groups that have a high content of these polyphenols, such as fruits, vegetables, oilseeds, grains, beverages (such as red wine, green tea and black tea), and dark chocolate. Table 1 summarizes the distribution of the major flavonoid classes among commonly consumed plant-based foods.

Table 1. Major dietary sources of flavonoids from different classes.

Flavonoid Class	Main Food Sources
Flavanones	Citrus fruits: grapefruit, orange, lemon, lime
Flavanols	Apricots, peaches, plums, pecans, cherries
Isoflavones	Soybeans, chickpeas
Flavones	Broccoli, celery, lettuce, onions, parsley, carrots, bell peppers; chamomile tea
Flavonols	Asparagus, leeks, kale, broccoli, onions
Flavones + Flavanols	Apples
Flavones + Flavonols	Olives
Flavonols + Flavanols	Cocoa (chocolate)
Flavonols + Catechins	Green tea
Flavones + Flavonols + Anthocyanins	Raspberries, blackberries, cherries, strawberries
Anthocyanins + Flavones	Grapes
Anthocyanins	Red cabbage, tomatoes, eggplant

Note: Some foods contain multiple classes of flavonoids, reflecting the diversity of bioactive compounds present in plant-based foods [14,21–29].

3.1.2. Estimated Intake and Variability Among Populations

Dietary flavonoid intake varies among populations according to geographic, cultural, dietary, and socioeconomic factors, which influence the availability and consumption of flavonoid-rich foods. In Eastern populations, tea and soy are the main dietary sources, whereas fruits and wine contribute more substantially in Western diets. Higher flavonoid intake has been consistently associated with a reduced risk of cardiovascular diseases, cancer, oxidative stress, and age-related cognitive decline, largely due to their antioxidant capacity [10,14,23,30,31].

The flavonoid content of plant foods is influenced by multiple factors, including environmental conditions, plant developmental stage, genetic variability, cultivation practices, and food processing or preparation methods [32–34]. Controlled cultivation and genetic improvement, including genetic engineering, can enhance flavonoid accumulation and support the development of crops with higher flavonoid content [35,36].

Food handling and preparation, particularly thermal processing, can alter flavonoid content depending on temperature, heating time, processing technique, food matrix, and flavonoid structure. Thermal treatment may either increase flavonoid availability by releasing compounds from the food matrix or decrease their content through degradation or conversion into derivatives. To preserve flavonoid stability, mild processing technologies, such as microwave and radiofrequency heating, have been increasingly adopted due to their shorter treatment times and lower temperatures [34,37].

Besides temperature, other factors that can affect flavonoid content during food preparation are pH, light, oxygen availability, and the presence of metal ions and enzymes. To improve flavonoid stability, innovative approaches including encapsulation, microencapsulation, lyophilization, and conjugation with biomacromolecules have been increasingly applied, particularly in processed foods [34].

Flavonoid content varies considerably among plant foods, ranging from a few milligrams to several hundred milligrams per 100 g. Strawberries contain 8.5–66.0 mg of anthocyanidins/100 g fresh weight, apples provide up to 33.6 mg of total flavonoids/100 g, and individual flavonoids, such as quercetin, may reach concentrations of up to 811.4 mg/100 g in specific foods [14,23].

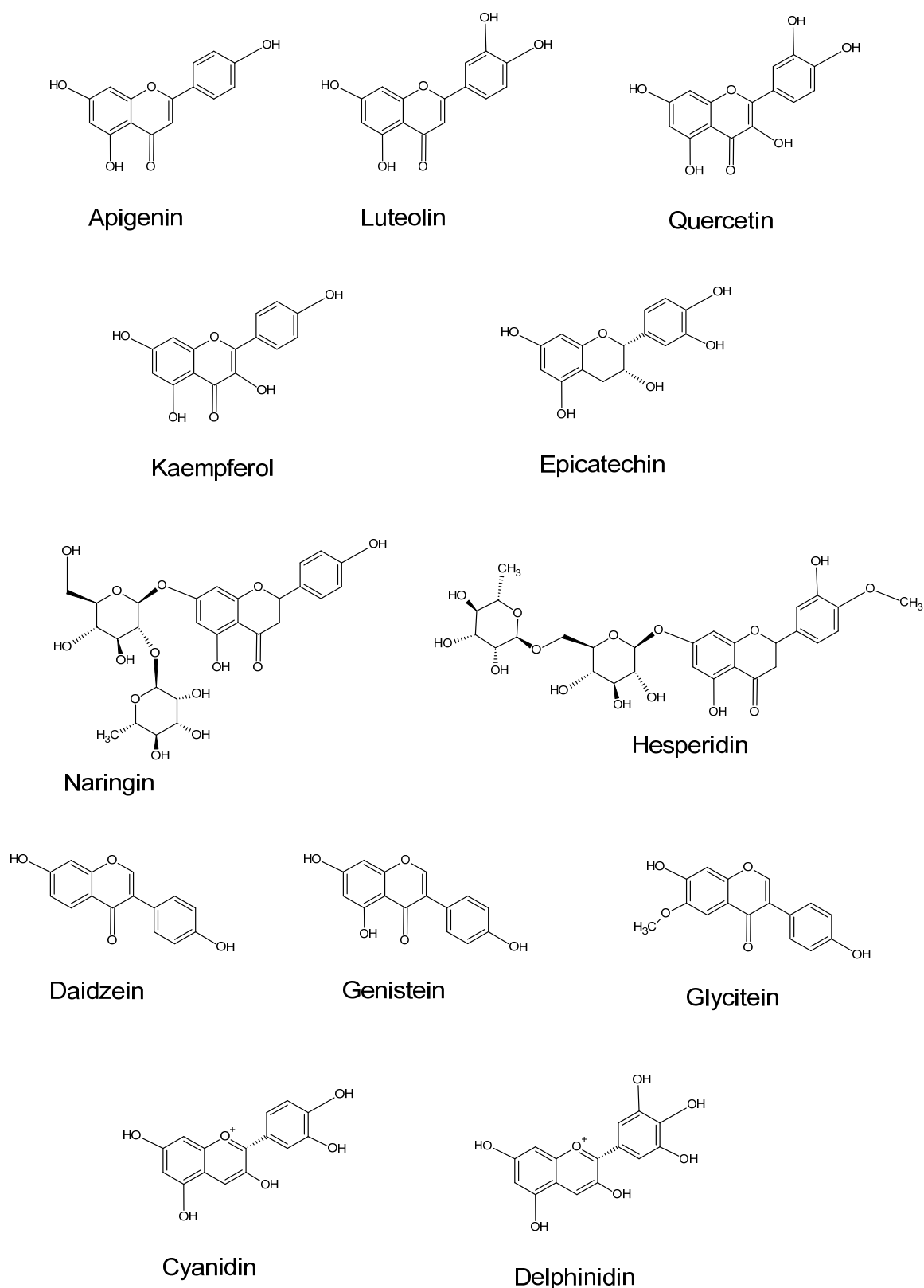


Figure 3. Examples of the main flavonoids commonly found in foods.

Dietary flavonoid intake varies substantially across populations due to differences in dietary patterns and food availability. Several studies illustrate this differences. In Oceania, the estimated intake is approximately 626 mg/day, with tea as the primary source [38]. In the Americas, Brazil's daily intake ranges from 60 to 106 mg, mainly from

lettuce, onion, chicory, arugula, oranges, and apples [39,40], whereas in the United States, intake ranges from 124 to 283 mg/day, with berries, grapes, oranges, apples, tea, wine, walnuts, and leafy vegetables as major contributors [41,42]. In Africa, flavonoid-rich foods include papaya, guava, pomegranate, African custard apple, pumpkin leaves, and beans; however, data on average daily flavonoid intake remain scarce [43,44]. In Europe, the average intake is approximately 428 mg/day, although Mediterranean countries show lower intakes, primarily derived from vegetables, nuts, berries, and wine [45,46]. In Asia, average flavonoid intake ranges from 165 mg/day in China to 318 mg/day in South Korea, with fruits (such as apples, tangerines, grapes, and watermelons) soy products, radishes, parsley, peppers, and onions representing important dietary sources [47,48].

Research on flavonoid intake indicates a wide variation in global consumption, depending on regional habits and the main food sources, such as teas, fruits, vegetables, and greens [30]. It is important to emphasize that the numbers presented reflect a reality that may change, depending on seasonal variations in the chemical composition of foods and behavioral variables of the population associated with age, sex, socioeconomic profile, and region of residence.

3.2. Flavonoid Absorption and Metabolism

3.2.1. Absorption, Bioavailability and Pharmacokinetics

Intestinal Absorption of Flavonoids and Influence of Glycosylation

Flavonoids usually have low oral bioavailability [49]. While aglycones are generally more lipophilic than corresponding glycosides, they are rarely found in this form in dietary sources of flavonoids. An important question that has recently been clarified is whether or not flavonoid glycosides can be absorbed intact without previously being hydrolyzed into the corresponding aglycones. It is now clear that some flavonoid glycosides can indeed be absorbed in the intestine. Thus, Wang et al. [50] were able to demonstrate that the brassica flavonoid quercetin 3-O-sophoroside (a diglycoside consisting of two glucose molecules joined by β -1,2 bonds) is absorbed intact after in situ administration of the glycoside in the rat jejunum. Using Caco-2 cell monolayers, Contreras et al. [51] were able to demonstrate using a sensitive nano-LC-TOF-MS method that both quercetin 3-O-glucoside and quercetin 3-O-glucuronide can be absorbed from the apical to the basolateral membrane of cells, albeit in a much lower proportion than quercetin. Similarly, pinocembrin-7-O- β -D-glucoside absorption in rats after oral administration was demonstrated, although the concentration of pinocembrin was about 4-fold higher than that of pinocembrin-7-O- β -D-glucoside after oral administration of the glucoside [52]. The double peak seen in the plasma concentration profile was interpreted as evidence of enterohepatic circulation of pinocembrin and pinocembrin-7-O- β -D-glucoside. Usually, glycosides have lower permeability than corresponding aglycones, as demonstrated in the work of Rastogi and Jana [53] which compared the permeability across Caco-2 cells of phenolic acids, trans-stilbenes, and flavonoids such as quercetin and chrysin, as well as rutin, a quercetin glycoside. From all tested compounds, rutin had the lower permeability. The type of glycosidic linkage is an important determinant of flavonoid disposition. Thus, O-glycosides may undergo hydrolysis during digestion whereas C-glycosides usually exhibit greater structural stability and altered metabolic behavior owing to the resistance of C-C glycosidic bonds to enzymatic and digestive cleavage [54].

Despite the limited available evidence of absorption as glycosides, the overwhelming evidence supports the view that the bioavailability of flavonoid glycosides is generally low and intestinal metabolism releases the corresponding aglycones after hydrolysis in the brush border of jejunum enterocytes by lactose phlorizin hydrolase and by cytosolic β -glycosidases. The deglycosylation occurs mainly in the jejunum, duodenum and ileum as

was demonstrated by a study investigating the absorption and metabolism of flavanone glycosides [55]. A recent study by Chow et al. [56] demonstrated that the absorption of flavonoid glycosides from hawthorn leaves through Caco-2 cells occurs through a combination of passive transport, active transport with involvement of the sodium-dependent glucose transporter, and also participation of gut microbiota to release the corresponding aglycones that are then absorbed through passive diffusion. The bioavailability of flavonoid glycosides also depends on the specific sugar moiety and even the linkage type. When luteolin 4'-O- α -glucoside and luteolin 4'-O- β -glucoside permeability across Caco-2 cell membranes were compared, the differences in permeability between these two isomeric glycosides were not significantly different [57]. However, luteolin 4'-O- β -glucoside was 2.4 times more effective in releasing luteolin to the basolateral side of the Caco-2 cells than the α anomer. Another important factor affecting bioavailability of flavonoids is molecular weight. The study by Pereira-Caro et al. [58] demonstrated that the bioavailability of flavan-3-ols from red wine or grape seed proanthocyanidin-rich extracts is strongly influenced by molecular weight and degree of polymerization, with lower-molecular-weight monomers and dimers showing greater systemic absorption, whereas larger oligomeric and polymeric proanthocyanidins were poorly absorbed and instead underwent extensive microbial metabolism in the gastrointestinal tract.

Although the permeability across membranes varies amongst flavonoids depending on the exact structural motifs present, passive diffusion alone cannot explain the large variability seen in oral bioavailability. Thus, there is evidence that intestinal absorption is strongly influenced also by the membrane transport system and presystemic metabolism.

Role of Transporters and Intestinal Metabolism in Determining Bioavailability

The absorption of flavonoids is increasingly viewed as a complex process resulting from the coordinated contributions of passive diffusion, metabolism and efflux transporters. The work by Bowles et al. [59] illustrates how the chemical structure determines the relative contributions of these processes. The work investigated the absorption of aspalathin, a C-glucosyl dihydrochalcone across Caco-2 monolayers, and showed very low permeability and no involvement of major glucose transporters or P-glycoprotein, suggesting predominantly paracellular passive transport. Despite this limited absorption, extensive Phase II metabolism was observed in vivo, with sulfated and glucuronidated metabolites detected in urine. When the transport of 30 flavonoids from different classes across the cell membrane of Caco-2 cells was compared with their cellular accumulation, no correlation was found [60]. This lack of correlation between permeability and cellular accumulation suggests that passive diffusion alone does not explain the absorption of these compounds. Indeed, some flavonoids exhibited a higher permeability from the basolateral to the apical side of the membrane, suggesting that efflux transporters are involved. The permeability of different flavonoid classes followed the order of flavanones $\geq$ isoflavones $>$ flavones $\geq$ chalcones $>$ flavonols. The complex interplay between passive diffusion, metabolism and efflux transporters that determine flavonoid absorption was the focus of the work by Li et al. [61]. In this interesting study, a combination of different experimental approaches was used, including in vitro enzymatic assays, live-cell confocal imaging, subcellular fractionation, and transporter inhibition and knockout models. The authors used kaempferol as a model compound, showing that it is rapidly absorbed and glucuronidated to a large extent by UGT1A9. However, the inhibition or deletion of efflux transporters, including P-glycoprotein, BCRP, and MRPs, led to an increase in intracellular aglycone levels and a concomitant decrease in glucuronide formation across subcellular compartments, indicating that glucuronidation is not an isolated metabolic process but is functionally dependent on transporter-mediated efflux,

as the removal of glucuronide conjugates is required to sustain metabolic flux. Similar glucuronidation–transport interplay has been demonstrated for bavachin, a prenylated flavanone, where extensive glucuronidation mediated predominantly by UGT1A1, UGT1A7, UGT1A8 and UGT1A9 was functionally coupled to transporter activity, with MRP4 identified as a major contributor to glucuronide efflux [62]. A similar relationship between metabolizing enzymes and transport proteins as factors determining the absorption and disposition has been described for other flavonoids, as is the case for naringin, hesperidin and their corresponding aglycones [63] and for the flavanone alpinetin [64]. Taken together, these studies demonstrate that intestinal bioavailability is determined by several interrelated processes including passive diffusion, transporter mediated influx and efflux, and rapid Phase II metabolism rather than permeability alone. The combined effects of all these processes are ultimately reflected in the observed pharmacokinetics profile of different flavonoids.

Pharmacokinetics Characteristics and Systemic Exposure

The complexity of intestinal absorption is reflected in systemic pharmacokinetic profiles, which consistently show low circulating levels of parent flavonoids and extensive metabolic transformation. Thus, in a human pharmacokinetics study [65] involving six healthy volunteers administered with a single oral dose of 500 mg aronia berry extract (a plant rich in anthocyanin glycosides), the $t_{\max}$ for anthocyanin glycosides varied from 1.60 to 2.67 h, and AUC values varied from 0.46 to 0.63 $\mu\text{g}\cdot\text{h}/\text{mL}$. The main metabolites detected in urine were ring-fission oxidation products such as ferulic and hippuric acid. In a similar human pharmacokinetic study involving 10 healthy male volunteers administered with 600 g of tomato puree [66], the levels of naringin (naringenin 7-O-rhamnoglucoside), naringenin, and naringenin-chalcone were evaluated. Both naringenin and naringenin-chalcone circulated in plasma mainly in the conjugated form (sulfate + glucuronide metabolites), and $t_{\max}$ was achieved after 3 h. Similarly, after an oral dose of 50 mg/Kg in rats, xanthohumol, a prenylated chalcone derived from hops, is rapidly absorbed ($t_{\max} = 3.0$ h), reaching a maximum plasma concentration of 85.56 ng/mL. Also, methylated, glucuronidated and oxidation products were detected, demonstrating both Phase I and Phase II metabolism [67]. In a comparative pharmacokinetic study of naringin and its metabolite naringenin involving rats, dogs and humans [68], a significant species-dependent effect was observed. Substantial first-pass metabolism limits the availability of naringin in humans and results in delayed absorption and prolonged excretion. Disease states can also influence absorption and pharmacokinetic parameters of flavonoids, such as demonstrated for rats with gastric ulcers [69]. In this work, the authors compared the pharmacokinetic parameters of five flavonoids present in “Shudage-4”, a herbal drug consisting of different plant extracts that was administered to normal rats and rats with experimentally induced gastric ulcers. The results show accelerated metabolism, lower systemic exposure (AUC), and reduced peak plasma concentrations ($C_{\max}$) attributed to a rapid concentration and consumption of these compounds directly at the gastrointestinal lesion.

Data concerning pharmacokinetic parameters for selected flavonoid compounds extracted from studies in the reviewed period are summarized in Table 2.

Systemic exposure is also determined by factors such as enterohepatic recycling and extrahepatic metabolism that together can impact the persistence and composition of the circulating flavonoid metabolites.

Table 2. Summary of pharmacokinetic parameters of selected flavonoids from in vivo studies identified during the period of the review.

Reference	Species Involved	Sample Detail and Dosing	Flavonoids and/or Metabolites Quantified	Pharmacokinetics Parameters Determined and Their Values	Analytical Technique Used
[70]	Humans	Isolated flavonoid (baicalein tablets); Doses of 200, 400, and 600 mg. Administered once daily on Days 1 and 10, and 3 times daily on Days 4–9.	Baicalein, baicalein-6-O-glucuronide (6-BG), baicalein-6-O-sulfate (6-BS), baicalein-7-O-glucuronide (7-BG), baicalein-7-O-sulfate (7-BS), baicalein-O-diglucuronide (BGG), baicalein-O-glucose-O-glucuronide (BGGLu), and methyl-O-baicalein-6-O-glucuronide (MeBG).	For 600 mg Baicalein (Day 10): $C_{max,ss} = 1322.50$ ng/mL; $t_{max} = 1.71$ h; $AUC_{0-t} = 12,384.96$ h*ng/mL; $t_{1/2z} = 11.29$ h.	LC-MS/MS operating in multiple reaction monitoring (MRM) mode.
[71]	Humans	Isolated flavonoid (baicalein tablets); Single ascending doses of 100, 200, 400, 600, 700, and 800 mg. A crossover food effect study was conducted using the 400 mg dose.	Baicalein, BGG, 6BG, 7BG, MeBG, BGGLu, 6BS, and 7BS.	For single doses (200, 400, 600, 800 mg Baicalein): $C_{max} = 280.44$, 628.80, 845.20, and 489.55 ng/mL; $AUC_{0-\infty} = 2035.57$, 2939.31, 4494.88, and 3754.43 h*ng/mL; $t_{1/2z}$ ranged from 7.80 to 14.91 h.	LC-MS/MS.
[72]	Rats (Male Sprague-Dawley)	Plant extract (<i>Anemarrhenae Rhizoma</i> extract); Oral gavage administration of 2 g/kg (2 mL/kg) extract.	Neomangiferin, mangiferin, timosaponin BII, timosaponin BIII, and timosaponin AIII.	Neomangiferin: $C_{max} = 35.36$ µg/L; $t_{max} = 6.33$ h; $AUC_{0-t} = 551.15$ µg*h/L; $t_{1/2} = 9.54$ h. Mangiferin: $C_{max} = 945.68$ µg/L; $t_{max} = 4.33$ h; $AUC_{0-t} = 15,897.84$ µg*h/L; $t_{1/2} = 10.60$ h.	UHPLC-MS/MS equipped with an electrospray ionization (ESI) source in negative-ion MRM mode.
[73]	Rats (Sprague-Dawley)	Isolated flavonoid (Phloretin-PHL) and its prodrug (TAPHL); Single oral doses of PHL (100, 200, 300 mg/kg) and equimolar doses of TAPHL (160, 320, 480 mg/kg).	Phloretin (PHL). (Note: TAPHL transformed into PHL in vivo, so only PHL was detected/quantified in the plasma).	PHL (100 mg/kg): $C_{max} = 952$ ng/mL; $t_{max} = 15$ min; $AUC_{0-t} = 141.5$ mg/L*min; $t_{1/2} = 241.4$ min. TAPHL (160 mg/kg): $C_{max} = 726$ ng/mL; $t_{max} = 260$ min; $AUC_{0-t} = 287.8$ mg/L*min; $t_{1/2} = 195.5$ min.	LC-MS/MS with negative ion ESI and MRM mode.
[74]	Humans	Plant extract (from whole sweet oranges, containing 28% naringenin and 8.5% naringin). Administered as single ascending naringenin doses of 150 mg, 300 mg, 600 mg, and 900 mg.	Naringenin (quantified in serum as total aglycone following β -glucuronidase/sulfatase enzymatic hydrolysis).	NAR 150 mg: $C_{max} = 15.76$ µM; $t_{max} = 3.17$ h; $AUC_{0-24h} = 67.61$ µM*h; $t_{1/2} = 3.0$ h. NAR 600 mg: $C_{max} = 48.45$ µM; $t_{max} = 2.41$ h; $AUC_{0-24h} = 199.06$ µM*h; $t_{1/2} = 2.65$ h.	LC-MS analyzed using MAVEN software.
[75]	Rats (Wistar normal and STZ-induced Type 2 Diabetes [T2D] rats)	Isolated flavonoid (Phlorizin-PHZ). Administered via oral gavage (50, 100, 200 mg/kg for T2D; 100 mg/kg for normal) and intravenous injection.	Parent phlorizin (PHZ), phloretin (PHT), total phlorizin (TPHZ), and total phloretin (TPHT). Quantified before and after enzymatic hydrolysis with β -glucuronidase and sulfatase.	Oral TPHT (100 mg/kg dose): $C_{max} = 24.63$ mg/L (T2D) vs. 8.84 mg/L (Normal); $AUC_{0-t} = 31.64$ mg/L*h (T2D) vs. 15.28 mg/L*h (Normal). Absolute Oral Bioavailability: ~5.78% (T2D) vs. 0% (Normal).	HPLC with a photodiode array detector (UV 285 nm).
[76]	Rats (Male Sprague-Dawley)	Isolated flavonoid (Herbacetin); Single oral dose of 20 mg/kg, intravenous dose of 4 mg/kg.	Herbacetin, herbacetin-glucuronides, herbacetin-sulfates, herbacetin-methylates.	Herbacetin Oral (20 mg/kg): $t_{max} = 6.75$ min; F (bioavailability) = 1.32%. IV (4 mg/kg): $t_{1/2} = 11.9$ min; Clearance = 16.4 mL/kg/min.	UHPLC-MS/MS and LC-MSn (ion-trap).

Table 2. Cont.

Reference	Species Involved	Sample Detail and Dosing	Flavonoids and/or Metabolites Quantified	Pharmacokinetics Parameters Determined and Their Values	Analytical Technique Used
[77]	Rats (Male Sprague-Dawley)	Isolated flavonoid (Bavachinin); Single oral dose of 70 mg/kg, intravenous dose of 5 mg/kg.	Bavachinin (BVC).	Oral (70 mg/kg): $C_{\max} = 175.88 \text{ ng/mL}$; $t_{\max} = 0.68 \text{ h}$; $t_{1/2} = 2.27 \text{ h}$; $AUC_{0-t} = 701.36 \text{ ng}\cdot\text{h/mL}$; $F = 5.27\%$.	UHPLC-ESI-MS/MS and UHPLC-Q/TOF-MS.
[68]	Rats, Dogs, and Humans	Isolated flavonoid (Naringin); Oral ascending doses (Rats: 10.5–168 mg/kg; Dogs: 3.1–49.6 mg/kg; Humans: 40–480 mg) and intravenous doses.	Naringin, Naringenin (measured post-enzymatic hydrolysis).	Human Oral (160 mg): Naringin $C_{\max} = 5.14 \text{ ng/mL}$, $t_{\max} = 1.75 \text{ h}$; Naringenin $C_{\max} = 32.8 \text{ ng/mL}$, $t_{\max} = 8.25 \text{ h}$. Absolute F of Naringin: 44.1% (Rats), 34.4% (Dogs).	UHPLC- MS/MS and UHPLC/Q-TOF-MS.
[78]	Rats (Male Sprague-Dawley)	Isolated flavonoid (Apigenin and Apigenin-7-O-glucuronide [A7G]); Oral doses of 30 mg/kg (Apigenin) and 49.6 mg/kg (A7G); IV doses evaluated.	Apigenin, Apigenin-7-O-glucuronide (A7G).	Oral Apigenin (30 mg/kg): $F = 0.708\%$; $C_{\max} = 189 \text{ ng/mL}$. Oral A7G (49.6 mg/kg): $F = 12.1\%$. Systemic exposure (AUC) of apigenin was 14.3-fold higher after A7G administration compared to apigenin administration.	UHPLC-MS/MS.
[79]	Humans	Complex mixture/Plant extract (Brazilian green propolis capsules); Single oral dose of 360 mg.	Kaempferide, 6-Methoxykaempferide, Dihydrokaempferide, Kaempferol.	After enzymatic hydrolysis (Total forms): Kaempferide $C_{\max} = 84 \text{ nM}$; 6-Methoxykaempferide $C_{\max} = 34 \text{ nM}$; Dihydrokaempferide $C_{\max} = 45 \text{ nM}$; Kaempferol $C_{\max} = 14 \text{ nM}$.	LC-MS/MS (UHPLC equipped with Orbitrap MS).
[80]	Aged Rats (20-month-old Sprague-Dawley)	Isolated flavonoid (Naringin); Single oral dose of 42 mg/kg.	Naringin, total Naringenin.	Oral (42 mg/kg): Naringin $C_{\max} = 179.6 \text{ }\mu\text{g/L}$, $t_{\max} = 0.50 \text{ h}$, $t_{1/2} = 9.52 \text{ h}$; Total Naringenin $C_{\max} = 3520.6 \text{ }\mu\text{g/L}$, $t_{\max} = 8.83 \text{ h}$, $t_{1/2} = 3.18 \text{ h}$.	RRLC-QQQ-MS/MS (triple quadrupole) and UFLC-Q-TOF-MS/MS.
[81]	Rats (Sprague-Dawley)	Plant extract (Total flavonoid extract of <i>Herba Epimedii</i>); Single oral dose of 0.69 g/kg (equivalent to approx. 42 mg/kg icariin).	Ikariin.	Oral (42 mg/kg icariin): $AUC_{0-\infty} = 164.16 \text{ }\mu\text{g}\cdot\text{h/L}$; $t_{\max} = 0.46 \text{ h}$; $t_{1/2} = 3.15 \text{ h}$; $CL_z/F = 389.04 \text{ L/h/kg}$.	LC-MS/MS (API 4000+ triple quadrupole) and LTQ-Orbitrap XL MS.
[82]	Mice and Rats	Isolated flavonoid (Isoxanthohumol-IXA, >90% purity); Single oral dose of 50 mg/kg or 14-day repeated dosing of 30 mg/kg (Mice).	Isoxanthohumol (IXA), 8-prenylnaringenin (8-PN).	Mice Oral (50 mg/kg single dose): IXA $C_{\max} = 4.0 \text{ }\mu\text{M}$; $t_{\max} = 0.6 \text{ h}$; $AUC_{0-24\text{h}} = 18.2 \text{ }\mu\text{mol}\cdot\text{h/L}$.	HPLC with ultraviolet detection.
[83]	Rats (Sprague-Dawley, male)	Plasma; Single oral administration of 72 mg/kg of complanatuside.	Complanatuside (CPS), rhamnocitrin 3-O- β -glc (RNG), rhamnocitrin (RNC).	CPS: $C_{\max} = 119.15 \text{ ng/mL}$; $t_{\max} = 1.0 \text{ h}$; $t_{1/2} = 0.51 \text{ h}$; $AUC_{0-t} = 143.52 \text{ }\mu\text{g/L}\cdot\text{h}$; RNG: $C_{\max} = 111.64 \text{ ng/mL}$; $t_{\max} = 3.0 \text{ h}$; $t_{1/2} = 1.33 \text{ h}$; $AUC_{0-t} = 381.73 \text{ }\mu\text{g/L}\cdot\text{h}$; RNC: $C_{\max} = 1122.18 \text{ ng/mL}$; $t_{\max} = 5.33 \text{ h}$; $t_{1/2} = 4.15 \text{ h}$; $AUC_{0-t} = 6540.14 \text{ }\mu\text{g/L}\cdot\text{h}$	UHPLC-Q-TOF-MS/MS and LC-MS/MS.
[84]	Humans	Plasma (and urine for excretion); Single oral dose of 200 mg baicalein.	Baicalein (BA), baicalein-6-O-glucuronide (6BG), baicalein-7-O-glucuronide (7BG), baicalein-6-O-glucuronide-7-O-glucuronide (BGG), baicalein-6-O-glucoside-7-O-glucuronide (BGGlu), baicalein-6-O-methyl-7-O-glucuronide (MeBG), baicalein-6-O-sulfate (6BS), baicalein-7-O-sulfate (7BS).	BA: $C_{\max} = 199 \text{ ng/mL}$; $t_{\max} = 3.0 \text{ h}$; $t_{1/2} = 8.22 \text{ h}$; $AUC_{0-t} = 1340 \text{ h}\cdot\text{ng/mL}$; 6BG: $C_{\max} = 85.9 \text{ ng/mL}$; $AUC_{0-t} = 906 \text{ h}\cdot\text{ng/mL}$; 7BG: $C_{\max} = 160 \text{ ng/mL}$; $AUC_{0-t} = 1215 \text{ h}\cdot\text{ng/mL}$; BGG: $C_{\max} = 2250 \text{ ng/mL}$; $AUC_{0-t} = 25,612 \text{ h}\cdot\text{ng/mL}$; 7BS: $C_{\max} = 1627 \text{ ng/mL}$; $AUC_{0-t} = 10,149 \text{ h}\cdot\text{ng/mL}$ (Other metabolites, see paper).	HPLC-MS/MS (MPX TM -2 high-throughput column switch system coupled to a Qtrap 5500 MS).

Table 2. Cont.

Reference	Species Involved	Sample Detail and Dosing	Flavonoids and/or Metabolites Quantified	Pharmacokinetics Parameters Determined and Their Values	Analytical Technique Used
[85]	Rats (Sprague-Dawley, male and female)	Plasma; Single oral administration of 100 mg/kg of iridin.	Irigenin (major metabolite/aglycon of iridin, as parent iridin was undetectable after 2 h).	Irigenin: C_{max} : 22.2 ng/mL; t_{max} : 3.05 h; $t_{1/2}$: 5.64 h; AUC_{0-t} : 167 ng/mL·h; $AUC_{0-\infty}$: 176 ng/mL·h; MRT_{0-t} : 6.77 h; CL/F: 600 L/h/kg; V_z/F : 4920 L/kg	UHPLC/QqQ MS (UHPLC system coupled with triple quadrupole mass spectrometry).
[86]	Rats (Sprague-Dawley, male)	Plasma; Kaempferol, intravenous (i.v.) bolus at 1, 2, 4 mg/kg and oral (p.o.) at 5, 10, 20 mg/kg.	Kaempferol, 4-hydroxyphenylacetic acid (4-HPAA).	Kaempferol (i.v. 1–4 mg/kg): C_0 : 3880–13,270 µg/L; $t_{1/2}$: 3.01–4.05 min; $AUC_{0-\infty}$: 266–996 h·µg/L; CL: 4.00–5.77 L/h/kg; V_d : 0.341–0.414 L/kg; 4-HPAA (i.v. 1–4 mg/kg): C_0 : 3651–19,788 µg/L; $t_{1/2}$: 18.6–28.3 min; $AUC_{0-\infty}$: 1405–4134 h·µg/L; CL: 0.876–1.13 L/h/kg; V_d : 0.391–0.666 L/kg.	UHPLC-MS/MS (UHPLC system coupled to a triple quadrupole mass spectrometer).
[87]	Rats (Sprague-Dawley, male)	Plasma; Single oral administration of 48.51 mg/kg of pinostrobin.	Pinostrobin.	Pinostrobin: C_{max} : 53.034 ng/mL; t_{max} : 0.133 h; $t_{1/2}$: 4.047 h; AUC_{0-24h} : 721.659 ng/mL·h; $AUC_{0-\infty}$: 881.114 ng/mL·h; $MRT_{0-\infty}$: 5.906 h; CL: 126.278 L/h/kg; V_d : 627.480 L/kg.	UHPLC-LTQ orbitrap-MS/MS.
[88]	Rats (Sprague-Dawley, male)	Plasma; Single intravenous (i.v.) administration via the tail vein at a dose of 3.6 mL/kg of concentrated Kudiezi injection (KI).	Flavonoid Glycosides: Luteolin-7-O-β-D-gentiobioside (VI), luteolin-7-O-β-D-glucuronide (VII), luteolin-7-O-β-D-glucoside (VIII), apigenin-7-O-β-D-glucuronide (IX); (Study also quantified five phenolic acids including chlorogenic and caffeic acids).	VI: $t_{1/2}$: 0.23 h; AUC_{0-t} : 163.85 h·ng/mL; CL: 7.66 L/h/kg; V_d : 2.51 L/kg; $MRT_{0-\infty}$: 0.28 h; VII: $t_{1/2}$: 0.66 h; AUC_{0-t} : 671.81 h·ng/mL; CL: 5.73 L/h/kg; V_d : 5.30 L/kg; $MRT_{0-\infty}$: 0.30 h; VIII: $t_{1/2}$: 0.13 h; AUC_{0-t} : 29.49 h·ng/mL; CL: 8.25 L/h/kg; V_d : 1.51 L/kg; $MRT_{0-\infty}$: 0.11 h; IX: $t_{1/2}$: 0.07 h; AUC_{0-t} : 55.74 h·ng/mL; CL: 10.07 L/h/kg; V_d : 1.00 L/kg; $MRT_{0-\infty}$: 0.09 h; (Note: Phenolic acids showed much slower elimination: $t_{1/2}$ = 2.22–6.09 h).	HPLC-MS/MS Triple Quadrupole with ESI, MRM in negative ionization mode.
[89]	Rats (Sprague-Dawley, male and female)	Plasma; Single oral administration of an extract mixture of 2 g/kg of fruits of <i>Tetradium ruticarpum</i> (FTR) and 2 g/kg licorice (intragastric administration).	Flavonoids: Liquiritigenin (LIQN), liquiritin (LIQ), isoliquiritin (ILIQ). (Study also quantified three alkaloids including evodiamine and three terpenoids including limonin).	LIQN: C_{max} : 6.18 ng/mL; t_{max} : 3.69 h; $t_{1/2}$: 2.67 h; AUC_{0-t} : 22.13 ng·h/mL; MRT : 7.42 h; LIQ: C_{max} : 14.94 ng/mL; t_{max} : 1.13 h; $t_{1/2}$: 2.17 h; AUC_{0-t} : 60.99 ng·h/mL; MRT : 4.19 h; ILIQ: C_{max} : 1.57 ng/mL; t_{max} : 0.46 h; $t_{1/2}$: 1.61 h; AUC_{0-t} : 3.82 ng·h/mL; MRT : 3.30 h.	UHPLC-MS/MS (Triple Quadrupole mass spectrometer).

PK parameters abbreviations: C_{max} = maximum (peak) concentration; $C_{max,SS}$ = maximum steady state concentration; C_0 = concentration at time zero; t_{max} = time for reaching maximum (peak) concentration; $t_{1/2}$ = half-life $t_{1/2Z}$ = terminal phase half-life; AUC_{0-t} = area under curve from time zero to last measured concentration; $AUC_{0-\infty}$ = area under curve from time zero to infinity; MRT_{0-t} : mean retention time from time zero to the last measurable concentration; $MRT_{0-\infty}$: mean retention time from time zero to infinity; CL: clearance; V_d : volume of distribution at terminal phase; CL/F: apparent clearance; V_z/F : apparent volume of distribution.

Enterohepatic Circulation and Extrahepatic Metabolism

In addition to intestinal absorption, several lines of evidence demonstrate that extrahepatic metabolism plays a central role in determining systemic exposure to flavonoids and their metabolites. Thus, in the work of Zeng et al. [90], intestinal perfusion and portal vein

infusion models in rats were used to investigate the origin and disposition of flavonoid glucuronides in enterohepatic recycling. The authors used a combination of experimental approaches that included single-pass intestinal perfusion, simultaneous sampling of portal and systemic circulation, and direct portal infusion of preformed glucuronides. This allowed the authors to evaluate hepatic versus extrahepatic contributions to glucuronide formation. Unexpectedly, no increase in glucuronide levels were found after liver passage, and the aglycone supply to the liver was not compatible with the high biliary levels of glucuronides found, both indicating limited hepatic glucuronidation. Furthermore, more than 60% of infused glucuronides were rapidly excreted into bile. These findings support an alternative model in which glucuronides formed extrahepatically, particularly in the intestine, are taken up by the liver and directly excreted into bile, thereby maintaining enterohepatic recycling without requiring hepatic conjugation.

This view is also supported by the work of Jiang et al. [91] which investigated the relative contributions of hepatic and intestine metabolism of calycosine (an O-methylated isoflavone). In this work, an in vivo rat model was used combining oral administration with simultaneous quantification of calycosin and its metabolites in portal vein plasma, liver, and systemic circulation. The authors found that calycosin glucuronides were already predominant in portal vein plasma prior to hepatic first pass and, more importantly, that glucuronides remained the major circulating forms in systemic plasma, where their exposure exceeded that of the parent compound by several orders of magnitude. Extensive metabolism and limited bioavailability are also supported by a study using grape pomace (a complex mixture of polyphenols) in which both metabolized and original compounds were detected in intestinal tissues. This indicates that there is significant local accumulation and biological activity at the gut level despite limited absorption [92].

Additional insights into the intestinal metabolism of flavonoids are provided by the work of Houriet et al. [93] which explored the differences in the intestinal metabolism of O- and C- flavone glycosides. Using an ex vivo porcine jejunum model, the authors showed that O-glycosylated flavones are rapidly hydrolyzed to their corresponding aglycones, while C-glycosylated flavones are absorbed intact through transepithelial transport. These results are compatible with the view of intestinal metabolism as a major constraining factor to absorption, reinforcing its role in determining systemic exposure. The extrahepatic metabolism of C-glycosylated flavones from *Passiflora incarnata* using a Caco-2 cell monolayer model was the focus of the work by Tremmel et al. [94]. This work demonstrated the formation of sulfated and glucuronidated metabolites for a series of flavones C-glycosides including isovitexin, orientin, and isoorientin. However, the mass spectrometric characterization of some of these metabolites was later put into question [95]. Although studied to a lesser degree, the stomach has also been implicated in the metabolism of flavonoids, as demonstrated in the work of Orrego-Lagarón et al., who used LC/MS with an Orbitrap high-resolution mass spectrometer to study the distribution of naringenin in the stomach and colon [96]. The presence and availability of conjugated metabolites generated during intestinal and hepatic metabolism has attracted interest in determining whether these metabolites can be responsible for many of the biological effects traditionally attributed to parent compounds.

Biological Relevance of Circulating Metabolites

The idea that flavonoid bioavailability is mainly determined by circulating metabolites and by enterohepatic circulation of these metabolites has important implications for the biological activity of flavonoids. This view is supported by the work of Kalt et al. [97]. In this work, human volunteers were enrolled in an intervention study with detection of urine metabolite levels used to investigate the bioavailability, metabolic fate, and disposition

of anthocyanins under different dosing regimens and intake durations. Volunteers were submitted to an anthocyanin-free run-in period, followed by 28 days of daily blueberry juice consumption and a subsequent washout phase. Repeated 24 h urine samples were collected and analyzed by LC-MS/MS to quantify parent compounds and a wide range of flavonoid-derived metabolites. The authors found that parent anthocyanins accounted for only a small fraction of total excreted compounds (~5%), while a large and complex pool of metabolites predominated, and that these metabolites persisted in urine even after several days of dietary washout.

In line with this view, studies directed towards the biological effects of flavonoid metabolites are increasingly being conducted. In an elegant recent work by Carecho et al. [98], the transport and biological effects of low-molecular-weight phenolic metabolites derived from polyphenols on the blood–brain barrier (BBB) were evaluated. Pyrogallol sulfate, resorcinol sulfate and phloroglucinol sulfate were investigated using a human brain microvascular endothelial cell transwell model. Their permeability from the apical to the basolateral compartment was assessed, with pyrogallol sulfate displaying the highest apparent permeability at physiological concentrations. Pyrogallol sulfate also increased membrane-associated β -catenin expression and reduced zonula occludens-1 membrane gaps, an indication of increased BBB integrity. In vivo, following intravenous injection in rats, all three metabolites were rapidly detected not only in blood and urine but also in brain tissue, reaching concentrations above basal levels as early as 15 s post-injection. Based on their results, the authors suggest that BBB transport may involve some form of active transport. This transport is likely to include caveolae-mediated transcytosis, since an increase in caveolin-1 expression and caveolae formation in endothelial cells was detected upon exposure to the flavonoid metabolite.

The hypouricemic activity of apigenin metabolites (from both Phase I and Phase II) was suggested by a recent work from Hsu et al., in which apigenin transport and metabolism was studied in an in vitro system consisting of a co-culture of Caco-2 and HepG2 cells arranged as monolayers in an insert designed to mimic an enterohepatic environment. Results showed that compounds were extensively metabolized by both the intestinal and liver cells. Using both mass balance considerations and network pharmacology analysis, the authors suggested that apigenin metabolites may be involved in hypouricemic activity [99].

Despite the growing realization that conjugated and microbiota-derived metabolites contribute to the biological effects traditionally attributed to parent flavonoids, the mechanisms underlying these effects remain incompletely understood. Current evidence suggests that these metabolites may exert biological activity through a number of mechanisms, including direct interactions with molecular targets, tissue-specific accumulation, modulation of cellular signaling pathways, or deconjugation at sites of inflammation. However, the biological activity of individual metabolites varies considerably according to their chemical structure, concentration, tissue distribution, and local enzymatic environment. A comprehensive discussion of these pharmacological aspects is beyond the scope of the present review, which focuses primarily on the metabolic fate of flavonoids and the implications of these metabolic transformations for their biological actions.

3.2.2. Phase I and Phase II Metabolism of Flavonoids

Flavonoid metabolism, once considered predominantly a hepatic process occurring after intestinal absorption, is now understood as a dynamic, multi-site process that takes place during absorption (intestinal metabolism), after absorption (hepatic metabolism), and through enterohepatic recycling involving biliary excretion, microbial transformation, and reabsorption. In this context, the gut microbiota plays a key role in generating ring-fission flavonoid metabolites. Phase I metabolism of flavonoids, although generally limited in com-

parison with conjugation reactions, primarily involves cytochrome P450 (CYP) enzymes and results in functionalization reactions of several flavones and flavanones [100–103] (although not limited to these classes), mainly through oxidation processes including hydroxylation and demethylation. Phase I oxidation may also result in the formation of reactive intermediate species, as demonstrated for silymarin flavonolignans, where CYP3A4-mediated demethylation and hydroxylation produced reactive metabolites that were detected as glutathione conjugates. The authors suggest that the formation of reactive species can contribute to the inhibition of drug-metabolizing enzymes and be the mechanism behind some of the reported interactions of silymarin with other drugs [104]. Even minor structural differences may result in significant differences in Phase I metabolic fate as recently demonstrated by isoflavone-based positional isomers [105]. Hydrolysis reactions, such as deglycosylation catalyzed by bacterial and intestinal glycosidases, as well as brush-border enzymes such as lactase–phlorizin hydrolase (LPH), are also important for many flavonoid glycosides. In contrast, Phase II metabolism predominates and involves reactions catalyzed by UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and catechol-O-methyltransferases (COMT), resulting in glucuronide, sulfate, and methylated conjugates of flavonoids. Different Phase II reactions may occur in succession in the metabolism of flavonoids. One such example of sequential Phase II metabolism is demonstrated for baicalein, where catechol-O-methyltransferase (COMT)-mediated methylation facilitates subsequent UDP-glucuronosyltransferase (UGT)-dependent glucuronidation, highlighting coordinated conjugative pathways that may influence flavonoid metabolic fate and bioactivity [106]. Although less extensively studied than glucuronidation, sulfation is an important metabolic pathway for specific flavonoids. Human cytosolic sulfotransferases exhibit marked substrate specificity, as demonstrated for quercitrin, epicatechin, rutin, hesperetin, naringenin, apigenin, and acacetin; genetic polymorphisms, transporter interplay and extensive Phase II conjugation further contribute to the interindividual variability in flavonoid sulfation and metabolic disposition [107–110].

There are several experimental models for the study of flavonoid metabolism, including *in vitro* models such as human and animal liver or intestinal microsomes, recombinant microsomes often expressing single CYP-450 or UGT isoforms, human and animal hepatocytes, HepG2 cells (a human liver carcinoma cell line frequently used in metabolism studies), as well as *in vivo* metabolite identification strategies. While *in vitro* experimental models are the preferred way to identify specific enzymes and pathways involved in the metabolism of flavonoids, *in vivo* studies provide a more physiologically relevant overview of the relative importance of Phase I and Phase II metabolism of individual compounds but are more limited at identifying specific metabolizing enzyme isoforms. An interesting new experimental approach for the study of flavonoid metabolism is illustrated in the work of Yue et al. [111], who used an online electrochemical cell coupled with high-resolution mass spectrometric detection to generate and identify metabolites of five major Citrus flavonoids—naringenin, naringin, hesperetin, hesperidin, and nobiletin. The setup utilized a boron-doped diamond (BDD) working electrode to effectively induce oxidative Phase I reactions without the need for Cytochrome P450 enzymes and successfully simulated Phase II conjugation reactions through the continuous addition of glutathione.

Advances in separation techniques such as ultra-high-performance liquid chromatography (UHPLC) coupled with high-resolution mass spectrometry and dedicated data-processing software have enabled untargeted metabolomics studies in which a large number of metabolites can be simultaneously identified from *in vivo* administration to animals of complex samples such as plant extracts. In a sample of papers included in this review ($n = 108$), the majority of them (72.2%) used UHPLC as the main separation technique, with 21.3% using exclusively HPLC (Figure 4). The recent advances in high-resolution mass

spectrometry have greatly enhanced the capacity for untargeted metabolomics analysis, allowing comprehensive profiling of flavonoid-derived metabolites without prior knowledge of their identities. These approaches combine suspect screening workflows (where a list of predefined expected metabolites is screened based on known biotransformation pathways), accurate mass measurements, isotope pattern analysis, in silico biotransformation prediction, and MS/MS spectral matching. These approaches have greatly increased the number of metabolites that can be detected and annotated in complex biological matrices. However, definite and confident structural assignment of flavonoid metabolites remains a challenge in some cases, since many metabolites are positional isomers that generate similar fragmentation patterns and authentic reference standards are frequently unavailable. Consequently, complementary analytical strategies, including ion mobility spectrometry, diagnostic fragmentation analysis, and comparison with enzymatically generated metabolites, are increasingly being incorporated into metabolomics workflows to improve metabolite annotation and structural confidence. The identification of metabolites is usually based on a combination of full-scan data with mass fragmentation analysis, information dependent acquisition based on predicted mass to charge ratio of metabolites, mass defect filtering, and constant neutral loss scanning and parent ion scanning, usually integrated in proprietary software under different brand names. Additional computational data-handling strategies have further expanded metabolite characterization capabilities. According to data from Table 3 below, the mass analyzers that are mostly used in studies of comprehensive untargeted flavonoid metabolomics (including suspect screening) include time of flight (TOF) and orbitrap analyzers. These analyzers provide the very high mass resolution and accuracy required for comprehensive metabolite annotation. For example, a high-resolution MS/MS workflow using orbitrap high-resolution mass spectrometry combining Metabolic Pathway Extension searching (a computational metabolite prediction and feature-matching strategy based on predefined biotransformation reactions) with Parallel Reaction Monitoring (for targeted metabolite quantification) enabled systematic identification and relative quantification of flavonoid xenobiotic metabolites, allowing identification of 131 metabolites derived from nine flavonoid subclasses in tissue S9 incubates [112].

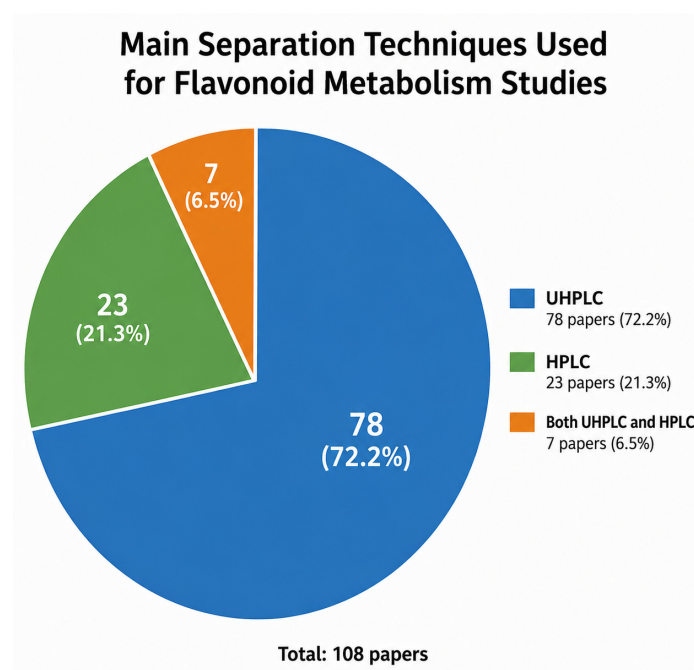


Figure 4. Distribution of main separation techniques by type in a sample of papers included in this review.

Several studies illustrate the power of these approaches. A total of 63 metabolites, including 27 baicalin-related Phase I and Phase II metabolites, were characterized following oral administration to rats of a mixture containing baicalin (a flavone glycoside), geniposide (an iridoid glycoside), and emodin (an anthraquinone) [113]. Using UHPLC/Q-TOF tandem mass spectrometry, a total of 138 xenobiotics (including metabolites and original drug constituents) were identified from plasma, urine, bile and feces of rats administered with a traditional Chinese medicine formula [114]. In a recent study [115], the metabolic fate of compounds from *Astragali Radix* was elucidated using UHPLC in tandem with Orbitrap high-resolution mass spectrometry. Employing a Mass Spectrometry Fragmentation Recursion Tree strategy, the authors managed to identify 208 xenobiotic compounds (including parent compounds) including several Phase I and II metabolites. Orbitrap high-resolution mass spectrometry as well as a hybrid triple quadrupole–linear ion trap MS/MS system was used to characterize metabolites as well as to quantify the main constituents of a traditional Chinese formula [116]. The main flavonoid metabolites identified were Phase II glucuronides and sulfate conjugates. Similar studies with extensive use of untargeted metabolite screening investigated metabolites derived from a variety of herbal drugs and preparations, including *Artemisia annua* [117], traditional Chinese formulas [118–129], *Smilax glabra* [130], *Scutellariae Radix* [131,132], *Abelmoschus manihot* [133,134], *Filifolium sibiricum* [135], *Moringa oleifera* seeds [136], Cupuassu, *Theobroma grandiflorum* [137] and propolis [138].

Besides the high resolving power of UHPLC with high-resolution mass spectrometry, other analytical advancements contribute to the elucidation of metabolic pathways. One of these analytical strategies is exemplified by the use of Ion Mobility Spectroscopy (IMS), a technique that separates ions in the gas phase based on their drift time in a neutral gas under the influence of an electric field. The drift time can be used to calculate the ion's collision cross-section, a measure of the ion's size and shape. This approach was developed [139] and then successfully applied [140] to elucidate the metabolic fate of the flavonol quercetin using both in vivo administration to human volunteers and two in vitro models (three-dimensional human small intestinal tissue model and HT29 intestinal cells).

When conducting in vivo studies using complex sample matrices such as plant extracts, one of the major obstacles is to distinguish parent sample components and endogenous compounds from true metabolites. Faced with this challenge in a recent study, authors used the Mass Spectrum-based Orthogonal Projection method (MSOP) [141]. The method consists of a post-acquisition chemometric strategy that uses orthogonal projection of LC–MS spectral matrices to selectively remove signals corresponding to parent herbal constituents from biological samples, thereby enhancing the detection and characterization of in vivo metabolites. The study was able to successfully identify several Phase I and Phase II metabolites of flavonoids after administration of *Oroxylum indicum* to rats.

The use of pure compounds administered in vivo, instead of complex mixtures, usually allows a more targeted study of flavonoid metabolism. The metabolism of icariin, a prenylated flavone glycoside used in traditional medicine for the treatment of osteoporosis, was studied. Icariin was administered to rats by gavage at a dose of 150 mg/kg [142]. The main metabolites detected included fourteen distinct compounds—driven principally by intestinal deglycosylation and subsequent hepatic glucuronidation—most notably the highly abundant secondary metabolite icariside II, the aglycone icaritin, and various novel demethylated or dehydroxylated glucuronide conjugates that are predominantly excreted via bile. Table 3 below summarizes additional in vivo metabolism studies conducted with isolated flavonoids found within the period covered by this review.

Table 3. Summary of main findings from in vivo metabolism studies of isolated flavonoids published in the period of this review.

Reference	Compounds Investigated and Dosing Details	Details of Experimental Approach	Main Findings Including Metabolites Identified and Enzymes Involved or Implied in the Metabolism	Analytical Technique Used
[143]	Sagittatoside B; Oral administration at 80 mg/kg.	In vivo: Rat plasma, bile, urine, and feces.	17 metabolites identified. Major pathways: hydrolysis, hydrogenation, hydroxylation, dehydrogenation, demethylation, decarbonylation, and conjugation with glucuronic acid and sugars.	UHPLC/Q-TOF-MS
[144]	Schaftoside; Single oral administration at 50 mg/kg.	In vivo: Plasma, urine, bile, feces from healthy and kidney stone model rats. In vitro: Intestinal bacteria.	28 metabolites (healthy) and 30 metabolites (model). Pathways: hydrolysis, hydrogenation, hydroxylation, oxidation, reduction, acetylation, methylation, and Phase II conjugation. Implied enzymes: β -D-glucosidase, methyltransferase, sulfotransferase, and acetyltransferase.	UHPLC-Q-TOF-MS/MS
[145]	Quercetin; Oral gavage at 50 and 100 mg/kg.	In vivo: Acute (up to 72 h) and long-term (20 weeks) feeding in rats, mice, and gerbils. Analyzed plasma, lungs, and liver.	Acute administration: Q3'S was the predominant metabolite in gerbils. Chronic administration: Q3G became the dominant metabolite in plasma, lung and liver of all species, followed by isorhamnetin (IH) and Q3'S. Gerbils showed the highest Q3'S conversion ratio. Enzymes induced: UDP-glucuronosyltransferase (UGT), phenolsulfotransferase (PST) and catechol-O-methyltransferase (COMT).	HPLC with UV spectrophotometric detection (370 nm)
[146]	Astilbin; Single oral administration by gavage at 250 mg/kg.	In vivo: Rat plasma (0.5–4 h), urine (0–24 h), and feces (0–24 h).	71 metabolites identified. Astilbin easily metabolized via intestinal alkaline environment. Principal pathways include ring cleavage, sulfation, dehydrogenation, methylation, hydroxylation, and glucuronidation.	UHPLC-Q-Exactive mass spectrometer (Orbitrap in negative ion mode)
[147]	Tangeretin; Intragastric administration at 250 mg/kg.	In vivo: Rat plasma, urine (0–24 h), and feces.	52 metabolites identified. Widespread demethylation to intermediate products. Other reactions include demethoxylation, hydroxylation, methoxylation, glucuronidation, glycosylation, and sulfation.	UHPLC-Q-Exactive Orbitrap-MS
[148]	3',4'-dimethoxy flavonol-3- β -D-glucopyranoside (DF3G); Oral administration at 50 mg/kg.	In vivo: Rat feces, urine, and bile.	Seven metabolites identified. Major metabolic pathways: deglycosylation, demethylation and glucuronidation. Hydrolysis was proposed as the initial metabolic step. Putative enzymes involved in deglycosylation: lactase-phlorizin hydrolase (LPH) and cytosolic β -glucosidase (CBG).	LC-ESI/MSn (Dionex Ultimate 3000 LC coupled to LCQ Fleet ion trap MS)
[149]	Eupatorin; Oral gavage at 50 mg/kg.	In vivo: Rat plasma, bile, urine, and feces. In vitro: Rat liver microsomes and intestinal flora.	51 metabolites identified in vivo and 60 metabolites identified in vitro. Main pathways: loss of CH ₂ , CH ₂ O, O and CO, oxidation, methylation, glucuronidation, sulfate conjugation, N-acetylation, hydrogenation, ketone formation, and glycine-, glutamine-, and glucose-conjugation.	UHPLC-Q-TOF-MS/MS (Shimadzu Nexera-X2 UHPLC coupled to triple TOF 5600+ MS/MS)

Table 3. Cont.

Reference	Compounds Investigated and Dosing Details	Details of Experimental Approach	Main Findings Including Metabolites Identified and Enzymes Involved or Implied in the Metabolism	Analytical Technique Used
[150]	Naringin; Single oral administration of 320 mg of naringin	In vivo: Urine and feces collected from human volunteers.	16 conjugated metabolites and 5 polyphenols identified. Extensive Phase II metabolism produced glucuronides, sulfates, glucuronide sulfates, and diglucuronides. Marked interindividual differences in metabolite profiles, excretion behavior, and metabolite types were observed.	UHPLC-Q-TOF-MS/MS
[151]	Isoliquiritigenin (ILG) & Isoliquiritin (ILQ); Oral gavage at 100 mg/kg/day for 8 days.	In vivo: Mice plasma, bile, urine, and feces.	25 ILG metabolites & 29 ILQ metabolites identified. Phase I: reduction, oxidation. Phase II: methylation, acetylation, glucosylation, glucuronidation, sulfation. Apigenin, luteolin, and quercetin were major related metabolites.	UHPLC-Q/TOF-MS/MS (Agilent 6550)
[152]	7, 8-dihydroxyflavone (7,8-DHF); Oral administration at 30 mg/kg daily for 8 months.	In vivo: Cynomolgus monkey plasma.	Conjugated forms are the main circulating metabolites. Pathways include methylation (mainly at the 8-position to form 7H8M-flavone), glucuronidation, and/or sulfation.	LC-MS/MS (Agilent 1200 LC coupled to Agilent 6460 triple quadrupole MS)
[153]	Icariin; Oral administration at 100 mg/kg/day for 3 days.	In vivo: Rat feces, urine, bile, and plasma.	25 metabolites identified. Principal pathways: hydroxylation and glucuronidation. Additional reactions included demethylation, dehydrogenation, epoxidation, reduction, and oxidation. Major circulating metabolites were M2, M14, M18, and M23, with epoxidation and reduction of the isopentenyl moiety reported as novel metabolic pathways.	UHPLC/Q-TOF-MS/MS
[154]	Luteolin-7-O-glucoside (L7G); Oral administration at 14 mg/kg at 12 h intervals for 2 weeks (or 3 consecutive days depending on experiment).	In vivo: Rat urine, plasma, bile, and feces.	44 metabolites identified. L7G is first hydrolyzed to luteolin. Phase I: hydrolysis, reduction (forming eriodictyol-related metabolites). Phase II: sulfation, glucuronidation, and methylation.	UHPLC/QTOFMS (ACQUITY UPLC I-Class)
[155]	Quercetin; Single oral administration at 80 mg/kg.	In vivo: Rat plasma, urine, feces, and bile.	36 metabolites identified. Phase I: reduction metabolites. Phase II: glucuronidation, sulfation, and methylation. Found high similarities between rat and human quercetin metabolism.	UHPLC-Q-TOF/MS (Acquity UHPLC coupled to Xevo G2-S QTOF MS)
[156]	Flavone-8-acetic acid (FAA); Intraperitoneal injection at 200 mg/kg.	In vivo: Mouse urine.	Directly undergoes Phase II metabolism (glucuronides). Formation of 6-OH-FAA was verified. Two FAA epoxides were scavenged by NAC and GSH forming corresponding adducts.	RP-HPLC with UV detection and MS (quadrupole ion-trap mass analyzer, LCQ-Advantage)
[157]	Hesperetin (HPT) & Hesperidin (HPD); Oral administration at 300 mg/Kg.	In vivo: Rat urine, plasma, and feces.	HPT and HPD share overlapping metabolic pathways in rats, predominantly undergoing glucuronidation, sulfation, demethylation, hydroxylation, and glycosylation.	UHPLC-LTQ-Orbitrap MSn (Dionex Ultimate 3000 UHPLC coupled to LTQ-Orbitrap XL)
[158]	Myricetin; Oral administration at 250 mg/kg.	In vivo: Rat urine, plasma, and feces.	38 metabolites identified. Pathways include glucuronidation, glucosylation, sulfation, dihydroxylation, acetylation, hydrogenation, and hydroxylation. A novel metabolite, 3,5-dihydroxybenzoic acid, was discovered.	UHPLC-Q-Exactive Orbitrap MS

Table 3. Cont.

Reference	Compounds Investigated and Dosing Details	Details of Experimental Approach	Main Findings Including Metabolites Identified and Enzymes Involved or Implied in the Metabolism	Analytical Technique Used
[159]	Morusin; Single oral administration at 16 mg/kg.	In vivo/In situ: Rat plasma, intestine, and bile. In vitro: Recombinant human UGTs, CYPs, and liver/intestinal microsomes.	Four mono-glucuronide metabolites identified (M-4'-G is the principal conjugate). CYP450 metabolites were negligible. UGT1A1, 1A3, 1A7, and 2B7 are the major active enzymes. Enterohepatic recycling heavily implied.	UHPLC with photodiode array and ESI(+)-Q-TOF-MS (Waters Acquity UPLC)
[160]	Silibinin capsule (Silibinins A and B); Oral administration at 50 and 100 mg/kg for rats, and single oral dose of 140 mg for humans.	In vivo: Rat and human urine.	18 metabolites identified. Glucuronide conjugates were the primary excretion form, followed by sulfated conjugates. Diglucuronides and 2,3-dehydro conjugates detected in humans but not rats.	UHPLC/Q-TOF-MS
[161]	Nobiletin (Nob); Oral administration using a sonde at 20 mg/kg.	In vivo: Rat plasma and tissue distribution (liver, heart, lungs, etc.).	Monodemethylation is the main metabolic pathway. 8-MDNob was identified as a novel metabolite, alongside the confirmation of 6-MDNob and 7-MDNob as in vivo oral metabolites.	UHPLC-MS/MS (triple quadrupole)
[162]	Diosmetin and Diosmin; Single oral (intra-gastric) administration (using a 30 mg/mL solution; exact dose in mg/kg not specified).	In vivo: rat plasma (collected from 0.5 to 6 h), urine (0–24 h), and feces (0–24 h).	46 diosmetin metabolites and 64 diosmin metabolites identified. Diosmetin was rapidly biotransformed and not detected in biological samples. Shared pathways include methylation, demethylation, hydroxylation, glycosylation, glucuronidation, diglucuronidation, and sulfation. Diosmin-specific pathways included demethoxylation, decarbonylation, dihydroxylation, and dehydroxylation. Excretion occurs primarily via urine due to dominant Phase II metabolism.	UHPLC-LTQ-Orbitrap MSn (Waters ACQUITY UPLC BEH C18 column coupled to an LTQ-Orbitrap XL mass spectrometer)
[163]	(–)-Epicatechin (EC); Single oral administration by gavage at 350 mg/kg.	In vivo: rat plasma (collected from 0.5 to 4 h), urine (0–24 h), feces (0–24 h), and tissue distribution (heart, liver, spleen, lung, kidney, and brain) collected 4 h post-dosing.	67 metabolites identified (67 in urine, 40 in feces, and 9 in blood). Reactions included methylation, dehydration, hydrogenation, glycosylation, sulfonation, glucuronidation, ring-cleavage, and composite reactions. The liver and kidneys were identified as the primary elimination organs. Researchers noted specific differences in metabolic behavior compared to its isomer, (+)-catechin.	UHPLC-LTQ-Orbitrap MS (Waters ACQUITY BEH C18 column coupled to an LTQ-Orbitrap mass spectrometer)

Human or animal liver and intestinal microsomes are widely used to elucidate both Phase I and Phase II metabolic pathways of specific flavonoids. Hydroxylation and demethylation (for O-methoxylated compounds) are two of the most frequent CYP-450 mediated Phase I transformations. Using rat liver microsomes combined with LC–ESI-MSⁿ (ion trap mass spectrometer) and chemical synthesis, the Phase I oxidative metabolism of bavachinin, a prenylated flavonoid, was studied. Extensive Phase I oxidative metabolism yielding eight metabolites, with hydroxylation and prenyl-chain oxidation, emerged as the predominant biotransformation pathways [164]. Using human liver microsomes, sakuranetin (7-O-methylnaringenin), an O-methoxylated flavanone, was shown to undergo CYP-mediated 7-O-demethylation to naringenin and subsequent hydroxylation to eriodictyol [165], while both parent compound and metabolites were additionally subjected to glucuronidation, illustrating how Phase I transformations may promote metabolic inter-conversion between flavonoids and generate substrates for Phase II conjugation. Using both

recombinant CYP-450 supersomes and liver microsomes, it was possible to identify CYP3A4 as the isoform responsible for the hydroxylation of the prenylated flavone morusin [166]. Using a similar experimental approach, CYP 2C9 and CYP2C19 were the main isoforms implicated in the metabolism of the chalcones loureirin A, loureirin B, and loureirin C and the flavones 7,4'-dihydroxyflavone and 5,7,4'-trihydroxyflavanone [167]. A combination of rat liver microsomes and in vivo administration of oroxin B by gavage (a flavone O-glycoside) was used to elucidate the complete metabolic fate of this flavonoid, which included nine biologically active metabolites amongst more than 30 identified [168]. One interesting strategy is the use of magnetic nanoparticles to immobilize microsomes, thus facilitating sample preparation (with the use of a magnetic field, the incubation medium is easily separated from the immobilized microsomes) and reutilization of the microsomes. Such an approach was used to study the metabolism of polymethoxylated flavonoids from *Citri reticulatae* by using rat microsomes immobilized in magnetic nanoparticles [169].

Flavonoids undergo extensive Phase II conjugation reactions, and liver microsomes are widely used to characterize these transformations. Thus, rat liver microsomes were used to identify sulfate, glucuronide and methyl conjugates of the flavonol galangin [170]. Indeed, glucuronidation is one of the main Phase II reactions of flavonoids. This view is confirmed by several studies. Extensive glucuronidation of kurarinone [171], a prenylated flavanone glycoside, was demonstrated in a study using human liver microsomes. Kurarinone forms two glucuronides upon incubation with liver microsomes, a reaction catalyzed mainly by UGT1A3 and UGT1A9, and glucuronidation decreases the cytotoxicity of the parent compound. The idea that glucuronidation may serve as a detoxifying reaction is also supported by a study of the methoxylated flavone nevadesin [172]. In this study, the authors were able to show that toxicity was attenuated exclusively in the glucuronidation-competent cell line, thus suggesting that Phase II glucuronide conjugation contributes to detoxification by reducing the biological activity of the parent compound. However, accumulating evidence indicates that flavonoid glucuronides may function not only as detoxification products but also as transport forms capable of regenerating active aglycones. Accordingly, the idea that flavonoid glucuronidation can be viewed as a dynamic process capable of regulating biological activity locally is supported by a study in which quercetin and quercetin-3-O-glucuronide underwent bidirectional intracellular metabolism in hypertrophied adipocytes, with both glucuronidation and β -glucuronidase-mediated deconjugation contributing to intracellular metabolite balance and antioxidant effects [173]. In one study, positional isomers of quercetin glucuronides displayed distinct stability and biological activity profiles while extracellular β -glucuronidase secreted by activated inflammatory macrophages released biologically active quercetin under inflammatory conditions [174]. However, the impact of Phase II metabolism on flavonoid bioactivity appears compound-dependent; for example, pectolinarigenin, a methoxylated flavone, undergoes extensive intestinal and hepatic glucuronidation to form pectolinarigenin-7-O-glucuronide [175], which exhibits diminished cytoprotective and metabolic regulatory activity relative to the parent aglycone, illustrating that conjugation can alter—rather than universally preserve or abolish—the biological properties of flavonoid metabolites.

The highest contribution of conjugative metabolism compared to Phase I reactions in the metabolism of flavonoids is also supported by a study investigating the metabolism of tiliroside, a flavonol glycoside. By using human hepatocytes combined with UHPLC-Q-Exactive Orbitrap high-resolution mass spectrometry, tiliroside was shown to undergo extensive metabolism with Phase II conjugation predominating, as glucuronidation and sulfation accounted for approximately 32% and 20% of detected metabolic transformations, respectively [176].

Using a combination of human liver microsomes and recombinant UGTs, a comprehensive study of the metabolism of genkwanin and hydroxygenkwanin was conducted [177]. The two flavones are present in *Daphne genkwa*, a plant used as a Chinese traditional medicine. The study identified a total of 29 metabolites, including demethylation, hydroxylation and O-glucuronidation as the main metabolic transformations. Recombinant UGTs allowed the identification of UGT1A1, UGT1A9 and UGT1A10 as the main isoforms involved in the formation of the glucuronides. The isoforms UGT1A3, UGT1A9 and UGT1A10 were also the main isoforms implicated in the glucuronidation of I-3, II-8 biapigenin, a biflavone used as dietary supplement [178]. The work used a combination of human liver microsomes and recombinant UGTs. UGT1A9 was also the main isoform implicated in the metabolism of licoricidin, a prenylated isoflavone [179].

Intestinal microsomes have also been used to study the metabolism of flavonoids, and glucuronidation is usually one of the main biotransformations detected when using this model. The glucuronidation of wushanicaritin, a prenylated flavonol isolated from *Epimedium* species used in Chinese traditional medicine, was studied using both liver as well as intestinal microsomes [180]. Two glucuronides of wushanicaritin were detected when the flavonol was incubated with intestinal or liver microsomes. The metabolism of another prenylated flavonol, icaritin, was similarly studied using a combined approach of liver and intestinal microsomes [181].

Flavonoid metabolism can be influenced by a number of factors, including enzyme expression, transporter activity and host physiology. Using HepG2 cells, Hashimoto et al. demonstrated [182] that quercetin undergoes extensive Phase II biotransformation and that metabolic conditions such as hyperglycaemia and exposure to cyanidin-3-glucoside reduced the formation of major quercetin conjugates, suggesting that physiological state and flavonoid–flavonoid interactions can modulate hepatic flavonoid metabolism.

3.2.3. Colonic and Bacterial Metabolism of Flavonoids

Due to their low bioavailability in the upper gastrointestinal tract, a significant proportion of the highly glycosylated or polymeric polyphenols are metabolized in the colon. It has been estimated that a substantial proportion of ingested polyphenols can reach the colon unmetabolized [183–186]; thus, colonic metabolism is an important aspect of flavonoid disposition. Even flavonoids that are absorbed in the small intestine and are metabolized in the liver can re-enter the colonic intestinal lumen via enterohepatic circulation [187,188]. Upon reaching the lower gut, a multitude of diverse bacterial microorganisms forming a local ecosystem will enzymatically modify parent compounds, usually resulting in low-molecular-weight fission-ring products that are more bioavailable than the original substrates and are biologically active, thus contributing to the alleged health benefits of polyphenols [189–192].

For the majority of glycosylated flavonoids, the first and usually the rate-limiting step of colonic bacterial metabolism is deglycosylation, a step that liberates aglycones for further metabolic transformation. Because of the limited availability of human glycosidase activity, this step is often dependent upon bacterial hydrolases such as β -glucosidases and α -rhamnosidases [183,187,193]. In support of this, it was shown that the gut microbiota can readily hydrolyse the isoflavone genistin into genistein [194], the flavone glycosides baicalin and wogonoside into baicalein and wogonin [185,190], and rutin and quercitrin into quercetin [193,195]. This capacity of the gut microbiota to hydrolyze flavonoid glycosides is severely impaired by experiments in which the bacterial ecosystem is altered. Thus, treatment of mice with an antibiotic cocktail capable of depleting all comensal bacteria markedly reduced phenolic metabolites serum concentrations compared to control mice [187], despite the two groups having similar serum concentrations of parent flavonoids. These results

demonstrate that colonic metabolism is essential for flavonoid metabolism even if it does not alter absorption. Similarly, depletion of gut microbiota by antibiotics prevented the hydrolysis of baicalin and wogonoside into their aglycones baicalein and wogonin [190]. This resulted in marked reduction in the production of metabolites and altered the pharmacokinetics of parent compounds, highlighting the importance of bacterial β -glucosidase in flavonoid biotransformation.

After deglycosilation, the released flavonoid aglycones can undergo extensive microbial degradation including C-ring fission, dehydroxylation, reduction, and demethylation [183,196–198]. These reactions result in a number of low-molecular-weight metabolites such as hydroxyphenylpropionic, hydroxyphenylacetic, hydroxybenzoic, and protocatechuic acids, but the exact array of ring-fission metabolites are compound-specific. However, metabolites that appear as common products across several flavonoid subclasses include 3-(4-hydroxyphenyl)propionic acid and p-hydroxyphenylacetic acid [187,189,197,199]. Accordingly, green tea catechins are mainly metabolized into phenylvalerolactones [200] while colonic metabolism of anthocyanins produce protocatechuic, syringic, and gallic acids [192]. These smaller phenolic products are usually more readily absorbed than their parent compounds. Supporting this concept, metabolites of genistin generated from gut microbiota were shown to be transported across a Caco-2 epithelial monolayer, with fourteen metabolites detected in the basolateral compartment [194].

As stressed before, the exact metabolic pathway a particular flavonoid will undergo depends largely on its chemical structure. While simple flavone and flavonol compounds are usually more rapidly metabolized, other compounds might demonstrate higher stability. Thus, in vitro fermentation reveals that silymarin flavonolignans are resistant to extensive microbial degradation. The main observed transformations were limited to demethylation and reduction pathways, and no evidence of metabolites usually associated with C-ring cleavage were detected [201]. By contrast, citrus flavonoids such as flavanone glycosides naringin and eriocitrin undergo extensive gut microbial metabolism, yielding compound-specific metabolites including neoeriocitrin and naringenin from naringin and eriodictyol and hesperetin from eriocitrin [202,203].

Age and disease states can influence the host gut microbiome and hence impact the diversity and the rate of metabolite production. However, health aging does not seem to alter the capacity of adults to metabolize flavonoids in the gut. Two studies in particular support this view. Lauwers et al. [197] demonstrated that gut microbiota from healthy young and elderly adults generated the same major olive polyphenol metabolites despite some differences in metabolite abundance and formation kinetics, whereas Alkhaldy et al. [204] observed differences attributed to age in urinary phenolic acid profiles after polyphenol intake but only limited differences in in vitro microbial flavonoid catabolism, suggesting that healthy aging modifies metabolite patterns rather than impairs gut flavonoid biotransformation capacity. The dysbiosis associated with some disease states can also impact colonic metabolism, although not in a predictable way. Thus, patients with Chron's disease [183] displayed reduced abundance of flavonoid-degrading bacteria (e.g., *Flavonifractor plautii*, *Eubacterium ramulus* and *Adlercreutzia equolifaciens*), lower abundance of flavonoid degradation genes, and markedly lower serum hippuric acid concentrations (0.44 vs. 1.18 μ M). In contrast, conditions like infectious diarrhea can lead to a faster metabolism of herbal formula secondary metabolites; for example, diarrheal piglets exhibited increased microbial β -glucosidase, β -glucuronidase, and nitroreductase activities associated with accelerated metabolism of flavonoids including daidzin, genistin, baicalin, and liquiritin [205].

There is an increasing realization that the metabolism of flavonoids by the gut microbiome can be in some cases a bidirectional event. Not only do gut microbes metabolize flavonoids into smaller bioactive compounds, but these compounds can in turn mod-

ify the gut microbiome, sometimes resulting in health-promoting effects. The work of Meng et al. [195] showed that quercitrin administration to mice generated 22 metabolites and markedly altered the gut microbiome, with higher beta-diversity and increases in the promotion of beneficial genera such as *Akkermansia* and *Lactococcus* and higher production of short-chain fatty acids that exerted improved intestinal barrier integrity and reduced inflammation. The effects on gut microbiome promoted by flavonoids and their metabolites are not universal. Particularly, the work of Vollmer et al. [191] used fecal microbiota obtained from three healthy human donors without gastrointestinal disease or recent antibiotic exposure to investigate the metabolism of flavonols and its glycosides (with both C- and O-glycosidic bonds). The authors found no significant changes in microbiota composition nor in the production of short-chain fatty acids associated with flavonoid treatment.

The microbial metabolites of flavonoids can exert several of the alleged pharmacological actions attributed to this class of compounds. Thus, 4-hydroxyphenylacetic acid (4-HPAA) has been shown to be able to reverse obesity-driven hepatic steatosis (MASLD) by activating hepatic AMP-activated protein kinase α (AMPK α) signaling, promoting transcriptional remodeling associated with fatty acid metabolism, reducing hepatic lipogenesis, and attenuating liver triglyceride accumulation and inflammation [206]. Liquiritigenin is converted into metabolites including daidigenin, a compound with reported antitumor activity, while eriocitrin and baicalein undergo extensive intestinal biotransformation yielding smaller phenolic metabolites and conjugated derivatives that may contribute to flavonoid bioactivity in vivo [188,207,208]. In summary, all these results strengthen the view that flavonoid metabolism by the gut microbiome is an important aspect of flavonoid disposition in vivo. Figure 5 below provides an overview of flavonoid metabolism as reviewed in this paper.

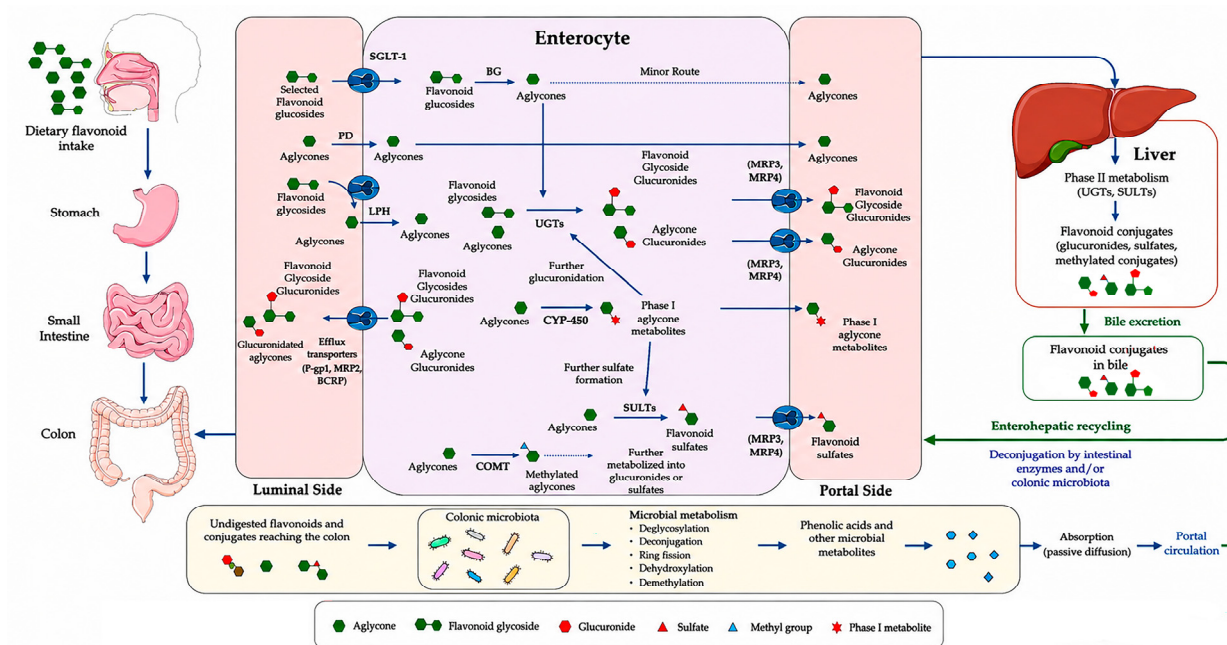


Figure 5. Overview of intestinal absorption and metabolism of flavonoids. Following dietary intake, flavonoids, predominantly present as glycosides, reach the small intestine. Selected flavonoid glycosides may be absorbed directly through mechanisms involving the sodium–glucose cotransporter 1 (SGLT1), whereas most flavonoid glycosides require hydrolysis prior to absorption, either at the brush border by lactase-phlorizin hydrolase (LPH) or intracellularly by cytosolic β -glucosidases (BG).

Aglycones readily cross the enterocyte membrane by passive diffusion (PD) and subsequently undergo extensive Phase I and Phase II metabolism. Glucuronidation, mediated by UDP-glucuronosyltransferases (UGTs), represents a major metabolic pathway in enterocytes. Although glucuronidation occurs predominantly on aglycones, direct glucuronidation of some flavonoid glycosides has also been reported. Emerging evidence suggests that glucuronidation is functionally coupled to glucuronide efflux, as transporter-mediated export of glucuronide conjugates through apical transporters (P-gp, MRP2 and BCRP) and basolateral transporters (MRP3 and MRP4) helps sustain metabolic flux by preventing intracellular accumulation of conjugates. Flavonoid aglycones may also undergo CYP450-mediated Phase I metabolism, generating metabolites that can either be transported across the enterocyte or undergo further Phase II conjugation, particularly glucuronidation by UGTs and sulfation by sulfotransferases (SULTs). In addition, flavonoids may be methylated by catechol-O-methyltransferases (COMT), producing methylated metabolites that frequently undergo subsequent glucuronidation and/or sulfation before entering the portal circulation. Upon reaching the liver through the portal vein, flavonoids and their metabolites may undergo additional Phase I and Phase II metabolism, including glucuronidation, sulfation and methylation. The resulting conjugates may subsequently enter the systemic circulation to reach target organs and tissues or be excreted into the bile. Biliary excretion of flavonoid conjugates enables enterohepatic recycling, through which glucuronides, sulfates and other conjugates are returned to the intestinal lumen, where they may be deconjugated by intestinal enzymes and/or members of the gut microbiota, regenerating absorbable metabolites that can undergo reabsorption. A substantial proportion of dietary flavonoids, together with biliary-derived conjugates, escapes absorption in the small intestine and reaches the colon. There, flavonoids are extensively metabolized by the gut microbiota through reactions including deglycosylation, deconjugation, ring fission, dehydroxylation, demethylation and reduction. These transformations generate a variety of low-molecular-weight phenolic acids and other microbial metabolites that may be absorbed into the portal circulation and contribute significantly to the systemic biological effects attributed to dietary flavonoids. Abbreviations: BG, β -glucosidase; BCRP, breast cancer resistance protein; COMT, catechol-O-methyltransferase; CYP450, cytochrome P450; LPH, lactase-phlorizin hydrolase; MRP, multidrug resistance-associated protein; P-gp, P-glycoprotein; PD, passive diffusion; SGLT1, sodium-glucose cotransporter 1; SULTs, sulfotransferases; UGTs, UDP-glucuronosyltransferases. This figure uses images provided by Servier Medical Art (<https://smart.servier.com>, accessed on 17 May 2026), licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>, accessed on 17 May 2026).

4. Current Challenges and Future Directions

Despite considerable effort in the area of flavonoid research and the progress in elucidating the metabolic fate of flavonoids, several important aspects remain unresolved. One of the main challenges is to determine the relative contributions of parent flavonoids and their circulating metabolites to the biological effects attributed to dietary flavonoid intake. Although in vitro and in vivo mechanistic studies frequently employ parent compounds, they generally reach the systemic circulation at low concentrations, whereas glucuronidated, sulfated, methylated and metabolites derived from gut microbiota constitute the predominant forms detected in biological fluids and tissues. Thus, a deeper and clearer understanding of the respective roles of parent compounds and metabolites is crucial for the correct interpretation of experimental and clinical studies. The apparent discrepancy between the consistent epidemiological data regarding the health benefits of flavonoids and their low systemic bioavailability indicates that future epidemiological studies should move beyond estimates of dietary flavonoid intake alone and incorporate measurements or predictions of circulating and tissue metabolites, although the methods for these predictions remain to be fully developed.

Another important area that deserves further research effort is the role of tissue-specific deconjugation of flavonoid metabolites and their role in local biological effects. A growing body of research demonstrates that glucuronidated and sulfated metabolites may

act as transport forms suffering local deconjugation through the action of enzymes such as β -glucuronidase, with the release of aglycones at sites of inflammation or tissue injury. More research should be conducted until the quantitative contribution of these local effects to the biological actions of flavonoids can be established.

A continuing area of research that can be expected to grow is the study of the pharmacology and the mechanism of action of different flavonoid metabolites. Although growing evidence indicates that many conjugated and microbiota-derived metabolites possess biological activity, their molecular targets, mechanisms of action, tissue distribution, and concentration–response relationships remain incompletely defined. Addressing these questions will be important to establish whether metabolites are merely reservoirs for parent compounds or constitute bioactive molecules in their own right.

Finally, a more comprehensive understanding of the structural determinants governing flavonoid bioavailability, metabolism and biological actions is needed, despite the past record of research in this area. Small structural differences, including glycosylation pattern, degree of hydroxylation, methylation, prenylation, and molecular size, can markedly influence intestinal absorption, transporter interactions, metabolic pathways, and tissue distribution. Establishing robust structure–metabolism–bioactivity relationships will facilitate the prediction of flavonoid disposition and support the rational development of dietary interventions and flavonoid-based nutraceuticals with improved biological efficacy.

5. Conclusions

The diverse biological actions of flavonoids and their widespread occurrence in the human diet have prompted major efforts to understand the relationship between intake, disposition, metabolism, and biological activity. Despite the low oral bioavailability of parent compounds, there is growing recognition that flavonoids may exert their biological actions through circulating metabolites. Flavonoids undergo extensive intestinal, hepatic, and microbial metabolism, resulting in circulating conjugated metabolites and a wide variety of low-molecular-weight microbial catabolites that may substantially contribute to their biological effects.

The literature reviewed over the past 10 years reveals that flavonoid disposition is the result of a complex array of events, including intestinal absorption, Phase I and Phase II metabolism, transporter-mediated efflux, enterohepatic recycling, and gut microbiota-mediated biotransformation. Several original studies support the idea that the intestine and gut microbiota act not as barriers but as an integral part of systemic exposure and biological activity promotion. To a lesser extent, some studies also show that many of the flavonoid metabolites exert important biological actions that were previously attributed exclusively to the parent compounds such as effects on inflammation, metabolic regulation, intestinal barrier integrity, and blood–brain barrier function.

Recent advances in separation sciences, especially ultra-high-performance liquid chromatography, together with high-resolution mass spectrometry, ion mobility spectrometry, and dedicated metabolomics software, have allowed increasingly sophisticated investigations of flavonoid metabolism. These techniques were employed in several studies of in vivo characterization of complex metabolic networks, including the simultaneous identification of large numbers of parent compounds and metabolites from complex botanical extracts. Future progress in the field will likely depend on the integration of untargeted metabolomics, gut microbiota analysis, and the increase in the use of computational tools and artificial intelligence-assisted data integration. These strategies will likely allow comprehensive characterization of flavonoid metabolic networks and identification of biologically active metabolites. In addition, a better understanding of interindividual variability in flavonoid metabolism, particularly those driven by microbiota-related differences and

host metabolic profile, will likely be important to the area of personalized nutrition. Together, these advancements should contribute to an improved understanding of the role of flavonoid metabolites in the promotion of the alleged health benefits of polyphenols.

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