Review

The role of dietary flavonoids for modulation of ATP binding cassette transporter mediated multidrug resistance

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ABSTRACT

Flavonoids are widely existing compounds with enormous pharmacological effects from food and medicine. However, the low bioavailability in intestinal absorption and metabolism limits their clinical application. Intestinal efflux ABC (ATP binding cassette) transporters, including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and multidrug resistance-associated proteins (MRPs), act as "pumping doors" to regulate the efflux of flavonoids from intestinal epithelial cells into the intestinal cavity or the systemic circulation. The present review describes the critical effect of ABC transporters involved in the efflux of flavonoids which depend on its efflux direction. And the role of flavonoids for modulation of intestinal ABC transporters was emphasized and several examples were given. We summarized that the resistance effect of flavonoid-mediated multidrug on ABC transporters may influence the bioavailability of drugs, bioactive ingredients and/or toxic compounds upon dietary uptake. Meanwhile, flavonoids functionalized as reversing agents of the ABC transporter may be an important mechanism for unexpected food-drug, food-toxin or food-food interactions. The overview also indicates that elucidation of the action and mechanism of the intestinal metabolic enzymes-efflux transporters coupling will lay a foundation for improving the bioavailability of flavonoids *in vivo* and increasing their clinical efficacy.

1. INTRODUCTION

Flavonoids distinguished by the main chemical structure of C6-C3-C6, are a class of polyphenols widely existed in food and other natural products. They have a variety of biological activities, such as antioxidant, anti-inflammatory, anti-virus, and anticancer effects. The instability of flavonoids in the intestinal is one of the reason for their low bioavailability, limiting their clinical application [1] . In recent years, the intestinal absorption and biotransformation characteristics of flavonoids have drawn extensive attentions. In general, flavonoids are metabolized by three phase II drug-metabolizing enzymes, including glucuronide transfer UDP glucuronosyltransferases (UGTs) [2], sulfatases (SULTs) [3], and glutathione S-transferases (GSTs) [4]. Subsequently, these phase II metabolites are transported by ATP binding cassettes Porter (ABC) located in the apical membrane of intestinal epithelial cells to the intestinal cavity or into systemic circulation, including P-glycoprotein (P-gp), mammary gland Cancer resistance protein (BCRP), and multidrug resistance associated protein (MDR-associated proteins, MRPs), etc. significantly affect the pharmacokinetics, drug interactions and clinical efficacy and side effects of flavonoids [5]. Studies have shown that phase II

metabolites are the main form of flavonoids that existed *in vivo*, while phase I drug metabolizing enzymes, alike cytochrome P450 (CYP) and etc., play a weak role in the internal disposal for flavonoids [6]. But it can be significantly affected by the efficient coupling of drug metabolizing enzymes with efflux transporters [7] . Recently published studies focusing on the coupling effect of phase I drug metabolizing enzyme of (CYP3A4)-P-gp, showed that the P-gp had a regulatory effect on CYP3A4 metabolism, and synergistically affected the pharmacokinetics and pharmacodynamics of drugs [8–10]. And our research group has recently found that there was an important coupling between phase II drug metabolizing enzymes (UGTs, sults) and efflux transporters (BCRP, MRPs), which significantly affected the in-vivo disposal of flavonoids [1, 11]. In this review, we summarized relative findings regarding the ABC transporters involved in the efflux of flavonoids from the intestinal cells to the basolateral blood side and thereby facilitating absorption, or back into the intestinal lumen, leading to reduced bioavailability.
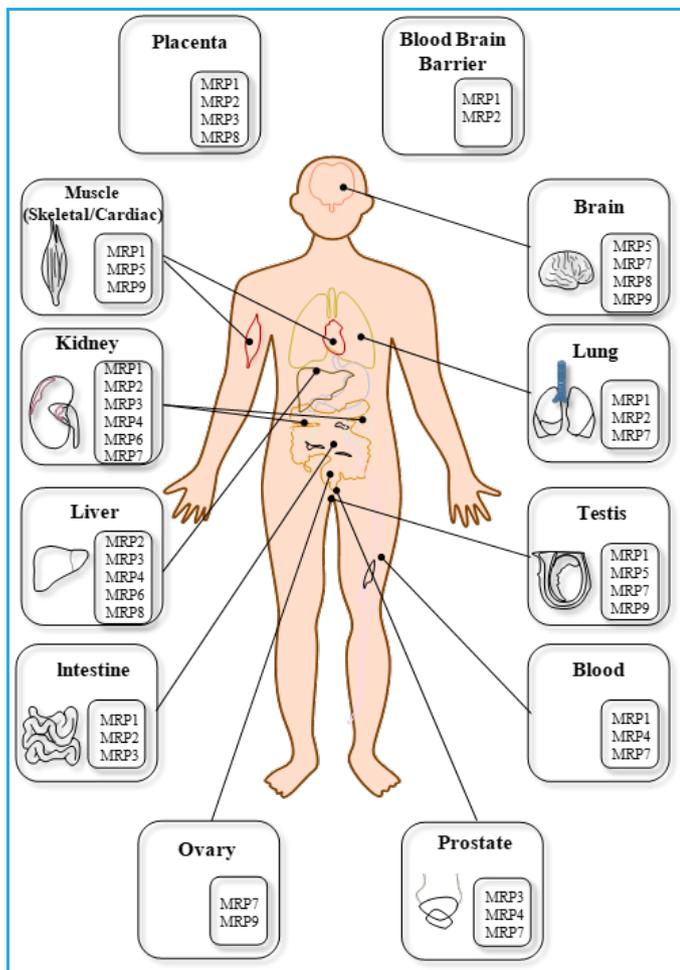
**Figure 1** | Distribution of MRPs in major human tissues and organs (Adapted from Wang et al., 2021).

2. CORRELATION BETWEEN ABC TRANSPORTERS AND MDR

The intestinal ABC transporters including P-gp (P-glycoprotein), MRPs (multidrug resistance proteins) and BCRP (breast cancer resistance protein) are involved in the efflux of chemicals [12]. These transporters are generally located specifically in the apical (intestinal luminal side) or basolateral (blood/plasma side) membrane of the enterocytes (**Figure 1**). Drugs could be simultaneously substrated and/or inhibited with more than one efflux transporter, indicating that these transporters exert a combined detoxification role in the intestine [13]. Among all of the ABC transporters, P-gp and MRPs have been extensively studied in controlling the efflux and uptake of many chemicals such as phenolics, nutrients, amino acids, inorganic ions, and etc. [14, 15]. Examples for the involvement of P-gp and MRPs in the bioavailability of phytochemicals and bioactive compounds can be found in literatures [16–18]. Several researchers conducted in-vitro studies and supported the role of ABC transporters in the absorption of drug at the gastrointestinal tract through monolayers of cultured Caco-2, HCT8, and MDCK epithelial cells [19–21]. Other *in vivo* works also demonstrated the P-gp

played an important part in reducing the oral bioavailability of several drugs, such as digoxin [22], talinolol [23], cyclosporine [24] and vinblastine [25]. And the result for the intestinal uptake of cyclosporine was also confirmed by healthy human [26]. More efficient transportation of saquinavir was found in MRP2-transfected MDCK II cells (Madin-Darby canine kidney), when compared to other MDCKII cells over-expressed ABC transporters, indicating a vital role of MRP2 in the efflux of saquinavir [27]. On the other hand, pharmacokinetic studies by Merino and co-workers [28] reported that the concentration of fluoroquinolone antibiotic ciprofloxacin in the plasma of deficient BRCP1 (-/-) mice was increased more than twofold (1.77 μg/ml), after the oral administration of ciprofloxacin in 10 mg/kg dose, as compared with wild-type mice (0.73 μg/ml, p < 0.01). This result suggested that the BCRP1 constrained the oral bioavailability of ciprofloxacin [28]. Meanwhile, the oral bioavailability of topotecan could also be affected by BRCP1 and P-gp transporters in mice [29]. In a study of co-administrated humans with GF120918, which was an inhibitor of BCRP and P-gp, the bioavailability of topotecan was increased as well [30]. In addition to the role of ABC transporters in the oral bioavailability of drugs, recent studies have focused on their roles in determining the bioavailability of toxins, bioactive compounds, and food ingredients [31, 32]. For example, 2-amino-1-methyl-6-phenylimidazo pyridine (PhIP) known as the major toxic heterocyclic amine in cooked meat, has been demonstrated to be transported back into the lumen by apical ABC transporters, when the ABC transporters acted as the first line of defense against this harmful compound [31]. The interaction between ABC transport proteins and PhIP was also investigated by using multiple model systems, including Caco-2 monolayers with specific inhibitors of Pgp- or MRP-associated transport proteins [33], MRP2 deficient rats [34], MRP2 knockout mice [35], and Bcrp1(-/-) mice [34]. Data obtained by Walle and co-workers from an *in vitro* Caco-2 cell monolayers system showed that MRP2 played a role in the transport of genistein-7-glucoside, and therefore resulted in a low bioavailability (Walle et al., 2003). The same system was employed for the transport studies of Ginkgo flavonols, and it was demonstrated that quercetin, kaempferol, and isorhamnetin were substrates for P-gp and that Pgp-mediated efflux [36]. Using the specific BCRP1 inhibitor of fumitremorgin C, in situ intestinal perfusion MRPs deficient rats and MDCKII cells, it was confirmed that especially Bcrp1 limited the absorption of quercetin from intestinal of the flavonoid [37]. In fact, the culture cells model, everted intestine, and the whole animal system are extensively used experimental methods for the evaluation of intestinal efflux transporters located on an apical membrane (**Figure 2**).

3. FLAVONOIDS REGULATE ABC TRANSPORTERS TO OVERCOME MDR

Phytoestrogen genistein has been demonstrated to modulate P-gp expression in hepatocellular carcinoma *in vitro*, moreover, it was found effective in the clearance of relevant P-gp substrates at concentrations as tested by (author?) [38]. In mouse macrophages J774.1, nobiletin activated AMPK and promoted the expression of ABCA1 and ABCG1 [39]. Tangeretin, a citrus pentamethoxyflavone, antagonized ABCB1-mediated multidrug resistance by inhibiting its transport function [40]. The effects of
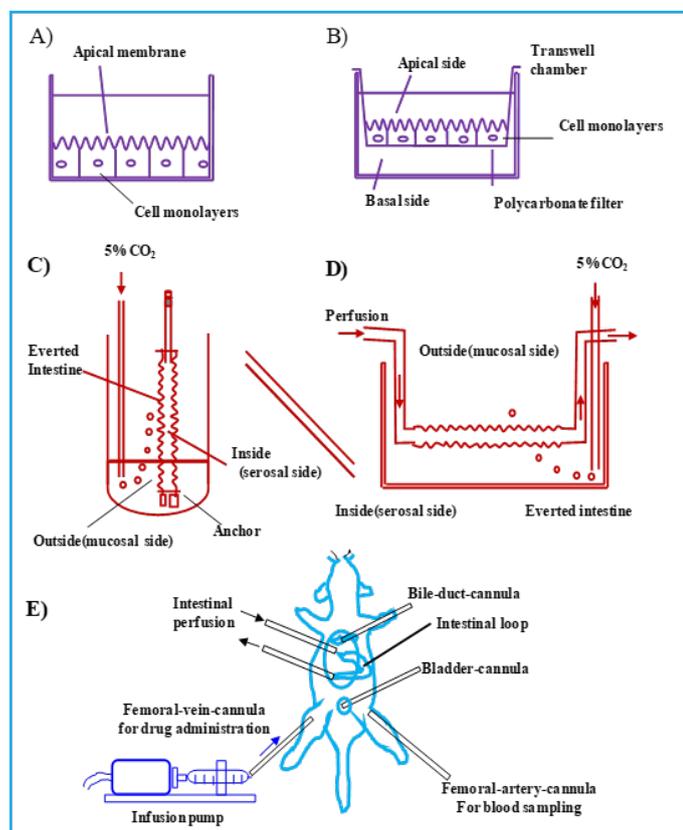
Figure 2 Schematic representation of some experimental methods for the functional analysis of intestinal efflux transporters located on apical membrane: culture cells (A,B), everted intestine (C, D), and whole animal (E), adapted from Takano et al [13] .

CG, EC, EGC, ECG, and EGCG on the P-gp function in multidrug-resistant P-gp over-expressed KB-C2 cells were observed by many researchers as shown in **Table 2**. Apigenin and naringenin with C2=C3 conjugation were proved to down-regulate ABC transporter expression, and inhibit P-gp activity and ATPase [41]. Ali and co-authors found that pre-treatment with naringin at 5 mg/kg body weight for 3 consecutive days, was able to inhibit the doxorubicin-stimulated ATPase activity and modulate the *in vivo* expression of P-gp [42]. The modulatory effect of acacetin-doxorubicin complex on the influx and efflux of doxorubicin was mediated through down-regulation of MDR1 transporter in NSCLC cells [43]. On the other hand, chrysin could inhibit ABCB1 mediated rhodamine 123 (an ABCB1 substrate) efflux in human breast cancer MDA-MB-231 cells [44]. Chrysin might also regulate ABCG2 mediated nitrofurantoin transport on ABCG2-overexpressed human MCF-7 breast cancer cells by increasing the area under the curve (AUC) [45]. Moreover, chrysin sensitized the ABCG2-transfected cells to mitoxantrone (an ABCG2 substrate) via stimulating ATPase [46]. Naringenin seemed to use an active ATP system mediated by MRP1, which was expressed at the basolateral side of the intestinal cell [47]. Daidzein (5 μM) could up-regulate MRP2- and down-regulate MRP1 protein expressions in MCF-7 and MDA-MB-231 cells, respectively. Major findings from both *in vitro* and *in vivo* studies revealed that the quercetin was an MDR modulator [48]. Biochanin A and phloretin have been
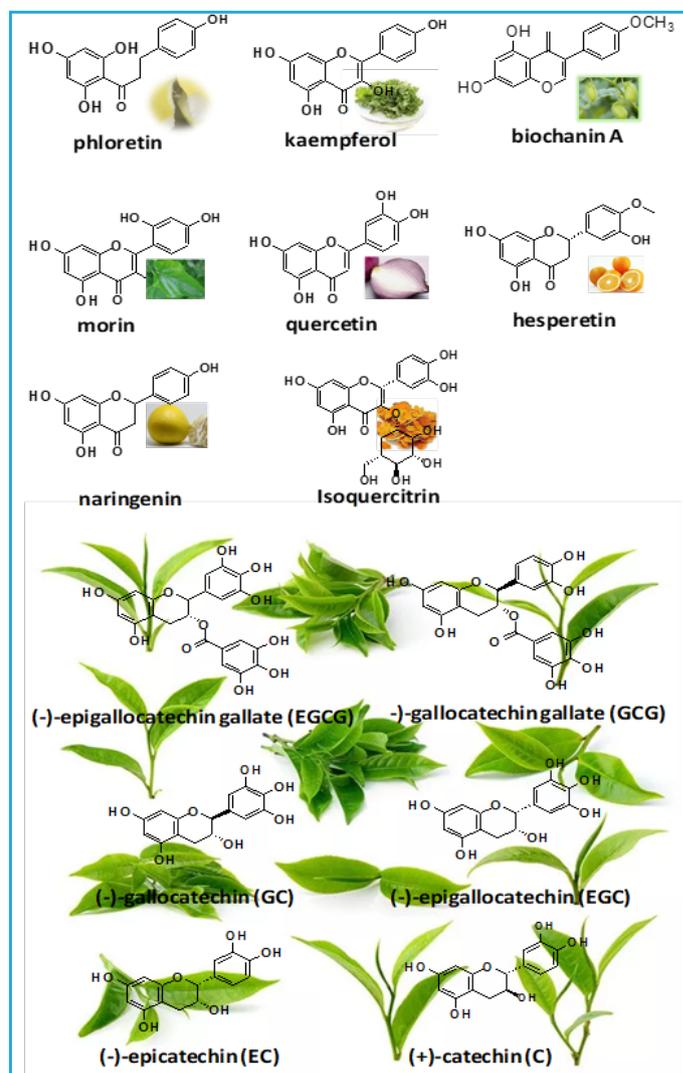

Figure 3 Chemical structure of some P-glycoprotein inhibitors belonging to flavonoids (PubChem Compound Database)

reported to have the ability to stimulate P-gp ATPase activity [49], however, morin and silymarin showed an inhibitory effect on P-gp, confirming that all of them could inhibit P-gp-mediated cellular efflux [50]. This review summarized the variety of flavonoids with an overlapped specificity for P-gp, MRPs, and BCRP as shown in **Figure 4**. Biochanin A, kaempferol hesperetin, and quercetin have been reported many times for their similar activities on ABC transporters, which indicated that the structural characteristics for the inhibition of the three major human ABC transporters(P-gp, BCRP and MRP2) may be partly similar. However, knowledge gained so far for the affinity overlap between ABC transporters has been only derived from scattered observations for individual compounds or small series [51, 52]. Therefore, more systematic studies on affinity patterns and molecular features of flavonoids that determine the inhibition specificity of ABC transporters are of great interest in future researches.

Table 1 Overview the effect of dietary flavonoids on transport or bioavailability of drugs and other xenobiotics in different model systems

| Flavonoids	Model system	Accumulation of target compound	References
Genistein	Caco-2, IEC-6, MDR1-MDCK, HCC-derived HepG2 cells	Repaglinide, Daunorubicin	[53, 54]
Morin, phloretin, biochanin A, chalcone, and silymarin	MCF-7/ADR cells	Daunomycin	[55]
Nobiletin	ABCB1 over-expressing A2780/T and A549/T, KB-C2 , Caco-2	Paclitaxel, doxorubicin, docetaxel, dounorubicin, daunorubicin, vinblastine	[56, 57]
Baicalein, (-)-epigallocatechin gallate, kaempferol, quercetin and silymarin	MDCK II	Rhodamine 123	[58]
Catechin-gallate, epigallocatechin-gallate, epicatechin-gallate	MDCK-MDR1 cells	Antiepileptic drugs: carbamazepine, phenytoin, oxcarbazepine	[58]
Curcumin	MCF‑7/DOX, MDA‑MB‑231/DOX	Doxorubicin	[59]
Quercetin,	Rats	Rhodamine 123	[60]
Acacetin, apigenin, chrysin, diosmetin, genistein, kaempferide, kaempferol, luteolin, luteolin-4'-O-glucoside, naringenin, naringenin-7-glucoside	K562, K562/BCRP	Mitoxantrone, SN-38, topotecan	[61]
Tangeretin	Adriamycin resistant human myelogenous leukemia	Vincristine, verapamil, cyclosporin A	[62]
Daidzein	LS-180V Cells	rhodamine-123	[63]
Biochanin-A, genistein, quercetin, chalcone, silymarin, phloretin, morin, and kaempferol	Panc-1 cells.	Daunomycin, vinblastine	[64]
Biochanin A, quercetin, silymarin	MCF-7, MCF-7 ADR	Daunomycin	[49]
Apigenin, biochanin A, chrysin, diosemin, fisetin, genistein, hesperitin, kaempferol, luteolin, morin, narigenin, phloretin, and quercetin	MDA-MB231	γ-hydroxybutyrate	[65]
Flavonoid derivatives possessing N-benzylpiperazine chain	K562/DOX cells	Doxorubicin	[66]
Myricetin	Caco-2	2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine	[67]
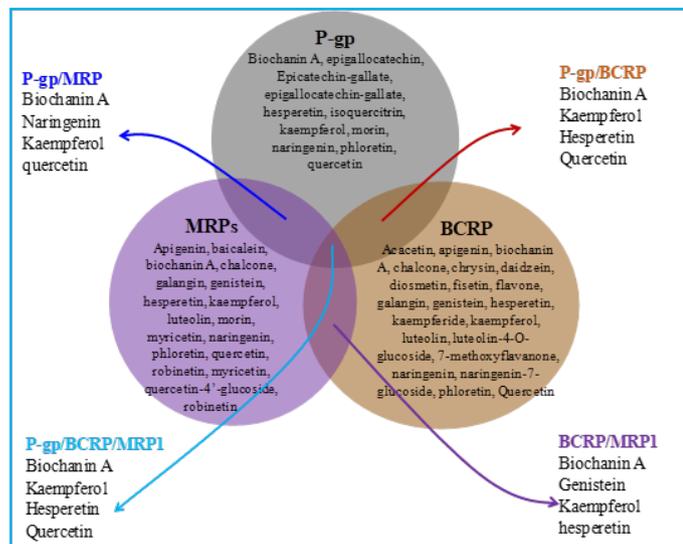
Figure 4 | A varieties of flavonoids with an overlapped specificity for P-gp, MRPs, and BCRP.

4. FLAVONOIDS EFFECT ON ACCUMULATION AND BIOAVAILABILITY OF BIOACTIVE COMPOUNDS

By given the involvement of transport proteins in the efficiency of intestinal transport, it can be envisaged that the ABC transport inhibitors may not only affect the MDR of tumor cells, but may also affect the bioavailability of diverse drugs, bioactive food ingredients and/or toxic compounds upon oral uptake (**Table 1**). For instance, Jin et al. found that exposure to genistein elicited an elevation in intracellular accumulations of Rhodamine 123 and daunorubicin (DNR) in P-gp-expressing cell lines [43]. Intestinal absorption of repaglinide was found predominantly enhanced by genistein or P-gp inhibitor of verapamil (Ver), according to in situ rat jejunal perfusion studies and *in vitro* transport assays using everted rat intestinal sac preparations [53]. Meanwhile, as P-gp inhibitors, morin, phloretin, biochanin A, chalcone, and silymarin, significantly increased daunomycin accumulation *in vitro* by more than 2.5-fold [55]. Moreover, it has been reported that nobiletin, a citrus methoxyflavone, could increase the accumulation of daunorubicin in KB-C2 cells and the uptake of vinblastine in Caco-2 cells. In addition, nobiletin significantly sensitized ABC overexpressed cells (A2780/T and A549/T) to paclitaxel, doxorubicin, docetaxel, and dounorubicin [56]. Ferreira and co-authors showed that baicalein, (-)-epigallocatechin gallate, kaempferol, quercetin and silymarin, at 200 μM, produced a significant enhancement in the intracellular accumulation of rhodamine 123 in MDCK-MDR1 cells potentially through the inhibition of P-gp activity [58] . They also evaluated a selected flavonoid combination of (-)-epigallocatechin gallate/silymarin in transepithelial transport experiments using licarbazepine (the active metabolite of oxcarbazepine) as a model compound, and the results revealed that the combination of (-)-epigallocatechin gallate/silymarin was the most promising one (Ferreira et al., 2018b). Furthermore, curcumin reversed doxorubicin resistance in human breast cancer MCF‐7/DOX and

MDA‐MB‐231/DOX cells by inhibiting the ATPase activity of ABCB4 [59]. Quercetin was another reported inhibitor for P-glycoprotein-mediated efflux transport, exhibiting an enhancement on the intracellular accumulation of rhodamine-123 in MCF-7/ADR cells with P-gp overexpressing [60]. Heptamethoxyflavone, nobiletin, and tangeretin, also promoted the uptake of vincristine in a concentration-dependent manner in adriamycin-resistant human myelogenous leukemia cells [62]. On the other hand, at the same concentration level of 100 μM, biochanin-A, genistein, quercetin, chalcone, silymarin, phloretin, morin, and kaempferol displayed the ability to increase the accumulation of daunomycin and vinblastine in Panc-1 cells [64]. Moreover, biochanin A, silymarin, and naringenin are able to reversethe MDR via inhibiting the P-gp function and increasing the accumulation of daunomycin in MCF-7/ADR cells [49]. Apigenin, biochanin A, chrysin, diosemin, fisetin, genistein, hesperitin, kaempferol, luteolin, morin, narigenin, phloretin, and quercetin significantly altered the pharmacokinetics and pharmacodynamics of γ-hydroxybutyrate [45]. Fan et al. (2019) investigated the inhibitory effects of 99 flavonoids on BCRP *in vitro* and *in vivo*, who clarified certain structure-activity relationships that might exist between flavonoids and BCRP. Eleven types of flavonoids, including amentoflavone, apigenin, biochanin A, chrysin, diosimin, genkwanin, hypericin, kaempferol, kaempferide, licochalcone A and naringenin, exhibited significant inhibition against BCRP in BCRP-MDCKII cells, through which the BCRP-mediated effluxes of doxorubicin and temozolomide were reduced (Fan et al., 2019). Moreover, another earlier study demonstrated that 28 flavonoid derivatives, at a concentration of 5 μM, increased the cytotoxic activity of doxorubicin in resistant K562/DOX cells [68]. Moreover, 2, 3, 4-trimethoxybenzylpiperazine chain attached to either flavones or flavanone moiety was found to be more potent in reversing the MDR as compared to the standard verapamil [67].
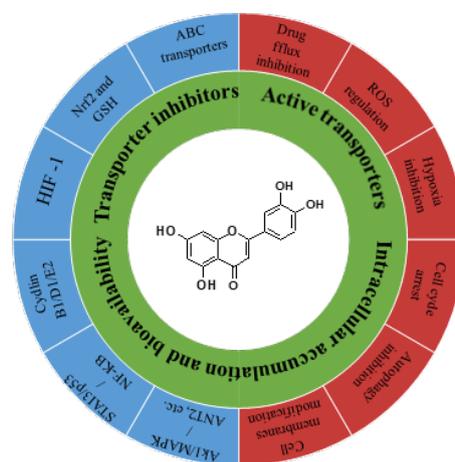
Figure 5 | Multi-functional flavonoids in overcoming MDR.

4.1. Molecular mechanism of flavonoids regulating ABC transporters

As in molecular level, the expression of P-gp is usually mediated by multiple pathways, involving CYP3A4, NF-κB, cylooxygenases-2 (COX-2), the mitogen-activated protein kinase (MAPK) pathway, and phosphoinositide 3-kinase (PI3K) (**Figure 5**). Among them, MAPK/ERK and NF-κB pathways are more reliable based on their molecular mechanisms for MDR inducement. The NF-κB pathway actively responds to MDR1 induction through the activation of IκB kinase, the degradation of IκB, and the generation of reactive oxygen species [69]. Moreover, NF-κB is bound at the nucleotide position of the MDR1 promoter mediating the transcription of MDR1 [70]. Similarly, the MAPK pathway, which involves in p38MAPK subfamilies, c-Jun NH2-terminal kinase (JNK)/stress-activate protein kinase (SAPK), and extracellular signal-regulated kinase (ERK), also has crucial parts in signals transmission, as provided by various kinds of stimulus to regulate the MDR1 expression. Currently, various studies revealed the over-expression of P-gp seemed to be closely related to the nuclear localization of Y-box binding protein 1(YB-1) in various solid tumors such as osteosarcoma, ovarian cancer, prostate cancer, and breast cancer [71]. In addition, Coles et al verified MAPK/ERK pathway regulated the phosphorylation of YB-1 via ERK phosphorylation [69]. However, the interaction between natural flavonoid agents and MAPK/ERK mediated YB-1 activity has not been well investigated yet.

4.2. NF-κB/IκB signaling pathway

Under normal physiological conditions, NF-κB and its antagonistic subunit IκB in cytoplasm will combine to form an inactive complex. When DNA is damaged by hypoxia or chemotherapeutic drugs, IκB is phosphorylated, and NF-κB will be released from the complex and enter the nucleus [72]. NF-κB could bind with the first exon of MDR1 promoter region and further start the transcription of MDR1, resulting in MDR [73]. For example, (**author?**) [69] used A2780 and paclitaxel resistant strain A2780/T to investigate the inhibitory effect of procyanidins on P-gp, and the result indicated that procyanidins could significantly enhance the cytotoxicity of paclitaxel in A2780/T resistant strain, and the procyanidins could also inhibit the expression of P-gp mRNA in time and concentration dependent manners [69]. In a study of signaling pathway, proanthocyanidins significantly inhibited the nuclear transfer of NF-κB/p65 induced by LPS and receptor activator for NF-κB ligand (RANKL), and attenuated the up regulation of NF-κB/IκB signaling pathway [69, 74]. In addition, puerarin also showed a reverse effect on drug resistance. After being treated with puerarin, the content of doxorubicin in K562/ADR resistant strain increased, and the IC$_{50}$ value of resistant strain decreased from 41.5 to 3.24 μM, and the expression of MDR1 protein, the activity of NF-κB in K562/ADR cells was significantly inhibited [55]. (**author?**) [75] proved that baicalein and luteolin have the chemoprevention effect and inhibit drug resistance of LoVo/Dx cells, which may be related to the overexpression of P-gp [75]. In addition, (**author?**) [70] have observed the ability of baicalein to suppress the activation of NF-κB in the HCT116 cell line. A significant increase in inflammation incidence of the tumor was also found in colon

tumors stimulated mice [70]. Furthermore, the survival of colon cancer cells and the stability of their genome were also influenced by baicalein through the reduction of securine level and the increase of γ-H2AX [76]. Taking these evidence together, (**author?**) [77] concluded that the underlying mechanisms of flavonoids with inhibitory effect on MDR in cancer cells may be due to the inhibition of p65 hydrolysis and IκB phosphorylation, thereby inhibiting the transcription and expression of MDR1, the target gene of NF-κB, and finally showing a protective effect on the drug resistance of drug-resistant cell lines (**Table 2**).

4.3. MAPK signaling pathway

There are three classical pathways in multicellular mammalian: extracellular signal regulated kinase (ERK), c-jun NH2 terminal kinase (JNK), and p38 MAPK pathway [86]. In MAPK signaling pathway, ERK pathway is mainly involved in cell proliferation and differentiation, while JNK and p38 pathways are mainly involved in cell stress response and apoptosis [87]. Meanwhile, JNK and p38 have high phosphorylation levels in tumor resistant cells [88]. Zhao and co-workers found proanthocyanidins inhibited the phosphorylation of JNK and p38 in A2780/T cells. Furthermore, proanthocyanidins effectively inhibited P-gp expression by blocking MDR1 gene transcription and increasing the intracellular accumulation of P-gp substrate rhodamine-123 [69]. Consistent with this result, quercetin reversed P-gp associated MDR by inhibiting the expression and function of P-gp through down-regulation of NF-κB activity and MAPK/ERK pathway as mediated YB-1 nuclear translocation (Chen et al.), offering an insight into the reversing mechanism of MDR by flavonoids. When cells are stimulated by anticancer drugs, YB-1 can translocate from cytoplasm to nucleus, specifically bind to the Y-box regulatory element of MDR1 gene promoter, inducing the expression of MDR1 gene [89]. In addition, the down-regulation in MDR1 mRNA and P-gp expression through MAPK/ERK pathway in MCF-7/ADR and K562/ADR could be also induced by different concentrations of dihydromyricetin (1, 5, 10 μM) [90]. (**author?**) [91] investigated the correlation between flavonoid paeonol and K562/doxorubicin drug-resistant cell line. They found the paeonol was effective in enhancing the concentration of intracellular drug. When doxorubicin was combined with paeonol, the reversal multiple was more than 20 times, and the expression of P-gp drug-resistant gene was significantly down regulated. The expression of p38 kinase in MAPK signaling pathway was also significantly decreased in drug-resistant cells treated with paeonol [68]. In exploring the effect of signal pathway on apoptosis rate, the results showed that p-ERK was significantly decreased after being treated with flavone and doxorubicin combination [92]. When cancer cells were exposed to chemotherapy drugs for a long time, P-gp mRNA dependence got increased. In terms of MAPK pathway, flavonoids may activate nuclear metastasis of YB-1 and reduce P-gp expression by inhibiting ERK1/2 phosphorylation [71]. In addition, p38 MAPK and Akt/MAPK in MAPK signaling pathway were upstream regulatory enzymes of NF-κB pathway, which could promote the phosphorylation of NF-κB and participate in the regulation of P-gp expression [93]. Flavonoids were also able to inhibit the expression of P-gp by inhibiting the phosphorylation of p38 [36].

Table 2 | Overview of literature on the effect of dietary flavonoids with MDR reversal effects and their application.

Flavonoids	Model system	Functions	References
Genistein	Rat, MCF-7, PC3 prostate cancer cells	ABC transporters regulation, ROS induction, NF-κB inhibition, modulates P-gp expression	[38, 78]
Nobiletin,	Mouse macrophages J774.1	ABC transporters regulation, activates AMPK	[39]
Tangeretin	Caco-2 cells	ABC transporters regulation, stimulates the ATPase activity	[40]
Catechin-gallate, epigallocatechin-gallate, epicatechin-gallate	KB-C2 cells and Caco-2 cells	Inhibits the efflux of P-gp substrates	[79, 80]
Quercetin	EPG85-257RDB cells	Decreases of P-gp expression, inhibit drug transport, down-regulates of ABCB1 gene expression	[81]
Apigenin, naringenin	Caco-2 cells	Downregulates ABC transporter, inhibits P-gp activity and ATPase	[41]
Kaempferol,	KB-3-1 cells (lacking Pgp)	Decreases of P-gp expression, inhibits P-gp activity	[82, 83]
Naringin	Sprague Dawley rats	ABC transporters regulation, inhibits the doxorubicin-stimulated ATPase activity, induction of GSH and GST, NF-κB inhibition, modulates P-gp expression	[42]
Acacetin	NSCLC cells	Downregulates MDR1 transporter	[43]
Chrysin	ABC-transfected cells, MDA-MB-231 cells	Sensitizes mitoxantrone, inhibit ABCB1 mediated rhodamine 123, ABC transporters regulation	[44–46]
Diosmetin, erythromycin	Staphylococcus aureus	Inhibit the growth of ABC-pump	[84]
Naringenin	Caco-2 cells	ABC transporters regulation	[47]
Daidzein, genistein	MCF-7, MDA-MB-231 cells	Inhibition of BCRP activity and sensitization to BCRP substrates	[85]
Biochanin A, phloretin	MCF-7, MDA435/LCC6	Stimulates P-gp ATPase activity, inhibits P-gp-mediated cellular efflux	[49, 50]
Morin, silymarin	MCF-7, MDA435/LCC6	Inhibits P-gp ATPase activity, inhibits P-gp-mediated cellular efflux	[50]

4.4. COX-2 signaling pathway

COX-2 is the source of reactive oxygen species (ROS). Excessive COX-2 can significantly increase the ROS level in cells, inducing oxidative stress. The concentration of ROS in tumor cells is significantly higher than that in normal cells [94]. When a high concentration of ROS poses a threat to cells' survival, the expression and clearance capacity of P-gp will increase in a stress manner to prevent our body from absorbing harmful substances and from being damaged by peroxidation [95]. Xiao and Co-authros **(author?)** [96] treated HL-60 and HL-60a resistant strains with quercetin for 48 h, and found that quercetin could induce apoptosis of both strains, and the apoptosis rate increased with the increase of quercetin concentration. The apoptosis rates of HL-60 and HL-60a cells, as well as the expression of COX-2 protein, were all correlated to P-gp mRNA and COX-2 mRNA [96], suggesting that flavonoids might induce apoptosis by inhibiting the expressions of COX-2 and P-gp and initiating caspase-3 cascade (; Breier et al., 2012) [97]. A further study showed that 10 μM apigenin combined with doxorubicin could reverse the IC50 value of ADM cells by 3.04 times and significantly increase the growth inhibition rate of bel-7401/ADM cells [98]. After apigenin treatment, the expression level of p-Akt was significantly down regulated (P < 0.01), suggesting that reversing effect of apigenin on drug resistance may be associated with inhibiting the expression of p-Akt [98]. Inhibition of Akt

can improve the drug resistance of cells. COX-2 and PI3K/Akt pathway belong to the upstream and downstream relationship, and glycogen synthase kinase 3β (GSK-3β) is the downstream protein of Akt [99]. Therefore, flavonoids may inhibit the expression of COX-2 and the phosphorylation of GSK-3β/β-Catenin to regulate the expression of downstream P-gp transcription factors. Another possible mechanism is the transcriptional activity that depends on the expressions of COX-2 and P-gp [100, 101].

4.5. GST-π pathway

GST is a class of enzymes that catalyze the binding of glutathione (GSH) with electrophilic substances in the body. Among their five subtypes, GST-π is closely related to tumor and has GSH binding site. Anticancer drugs can induce the increase of GST-π expression, catalyze the combination of GSH with chemotherapeutic drugs and be excreted out of cells, leading to the drug resistance [102]. Another study reported by Balyan and co-authors investigated the effect of luteolin on GST-π of K562/A02 drug-resistant cell line and found luteolin significantly reduced the GSH content in K562/A02 cells, and the expression of GST-π protein was decreased by 22%, 26% and 34% on day 1, 3 and 5, respectively [103]. It was speculated that the mechanism for some flavonoids to reverse drug resistance may be related to GST-π, mainly by inhibiting the

combination of anticancer drugs with GSH [104]. However, studies also supported that kaempferol [105] and hesperetin [106] could change the expressions of GST-π and P-gp in drug-resistant strains, and the mechanism of reversing MDR characteristics might be due to the inhibition in the change of P-gp expression induced by GST-π. Moreover, after quercetin treatment, the reversed multiple of Bel/Fu resistant strain could reach 2.4 times, and the expression of GST-π gene in cells could be significantly down regulated, and meanwhile, the ratio of P-gp/β-Catenin was decreased [36]. Xu and Co-authors **(author?)** [107] discussed the effect of Baicalin on the MDR characteristics of lung cancer cells A549 and its mechanism. The results indicated that the growth of lung cancer cells treated with baicalin was significantly inhibited in time and concentration dependent manners; the expression of MDR1 and GST-π mRNA in tumor cells treated with baicalin was significantly decreased [107]. When apigenin was combined with doxorubicin, the combination reduced the content of GST-π to 18% and the level of ROS increased by more than 20% compared to doxorubicin treatment [108]. GST-π, as an enzyme related to detoxification, is involved in the detoxification process of free radicals produced by oxidants and cytotoxic substances [109]. In this line, flavonoids may also inhibit the expression of GST-π by inhibiting the entry of nuclear factor E2 related factor 2 (Nrf2) into the nucleus and binding with the promoter of downstream target gene GST-π, thereby increasing the level of ROS involved in the tyrosine kinase signaling pathway as a second messenger and regulating the expression of P-gp [110].

5. DISPOSITION OF FLAVONOIDS IMPACTS THEIR EFFECT ON ABC TRANSPORTER

The disposition of flavonoids in the gastrointestinal tract after dietary digestion provided numerous promises for human health.

Correspondingly, the ability of flavonoids to shape the gastrointestinal tract offers the prospective of diet based therapies for a wide array of conditions associated with dysbiosis [111]. Actually, the flavonoids after ingestion will undergo a metabolic pathways in the small intestine to produce glycosides [11]. An enormous amount of the administrated flavonoids will be transported and converted into phenolic acids in the colon by microflora. Further transportation and metabolism through the hepatic portal vein often happened in the liver. As shown in **Figure 6**, phase I and phase II metabolism of flavonoids resulted in more polar compoundgeneration. The metabolites then reach the targeted tissues or are excreted by the kidneys. Many factors such as low solubility, high degradation rate, and low metabolism limit the bioavailability of flavonoids. Phase II enzymes such as uridine-5′-diphosphate glucuronosyltransferases (UGTs) and catechol-O- methyl transferases (COMT) are involved in extensive first pass metabolism of flavonoids by transforming them to more hydrophilic forms for excretion (Fernandes et al., 2016) [112]. As followed, the effluxes of flavonoids getting out of intestinal cells return to the lumen for excretion as modulated by ABC transporters, which also limits their bioavailability [113]. In another word, depending on their structure, flavonoids and their metabolites might act as inducers or inhibitors of ABC transporters and phase II metabolizing enzymes [114].
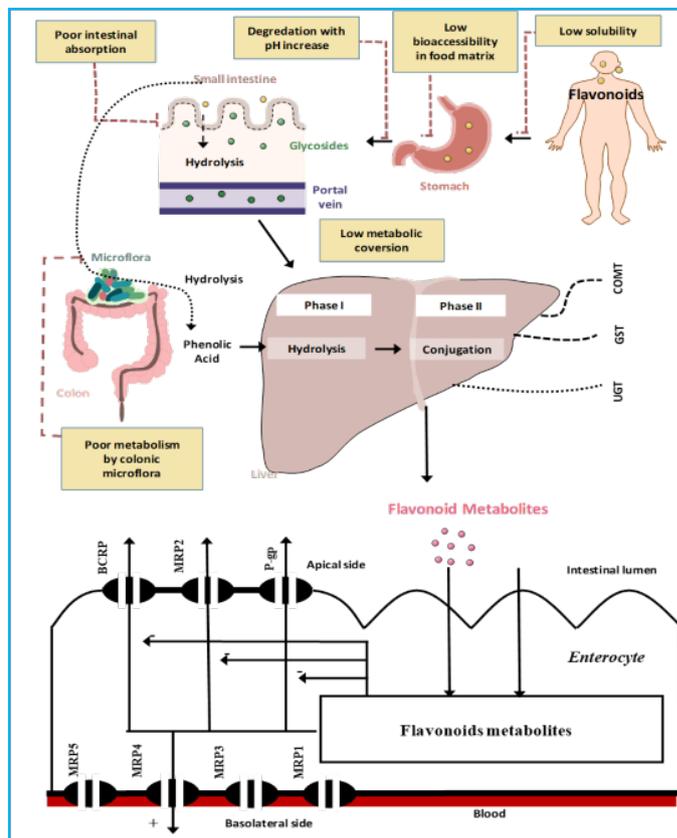
Figure 6 | Schematic representation of metabolism andfactors limiting the bioavailability of flavonoids. Abbreviations: UGT,UDP-glucuronosyltransferase; GST, glutathione S-transferase; COMT, catecholO-methyltransferase.

6. CONCLUSIONS

Researchers have shown the therapeutic effect of flavonoids in a variety of diseases, but its low bioavailability significantly limits its clinical application, which is closely related to intestinal absorption and metabolism. The absorption and metabolism mediated by intestinal phase II drug metabolizing enzymes (UGTs and SLUTs) and efflux transporters (P-gp, BCRP and MRPs) have attracted extensive attention and became a hot topic on the pharmacokinetics of flavonoids. Once being absorbed by intestinal epithelial cells, flavonoids would be widely used by phase II enzymes; meanwhile, drug metabolizing enzymes are coupled with efflux transporters to prevent their absorption. Therefore, the coupling of intestinal drug metabolizing enzymes with efflux transporters is considered as the main reason for the low bioavailability of flavonoids (e.g., genistein, daidzein, Robinia pseudoacacia, quercetin, kaempferol, chrysin and apigenin). it also forms hydrophilic metabolites (glucuronide/sulfate) catalyzed by phase II drug metabolizing enzymes UGTs and SLUTs, which cannot penetrate cell membrane by passive diffusion. The binding metabolites of these flavonoids are the substrates of BCRP and MRP2. The external transporters can regulate the rate of the extracellular glucuronide/sulfate, and then affect the formation of glucuronide/ sulfation, increasing the retention time of flavonoid compounds and glucuronides in the local intestine.

Table 3   nteractions between transporters and flavonoids. Adapt from Jiang and Hu, 2012

Transporters	Substrates	Flavonoids as modulators	Inhibitor
P-gp	Flavonoid aglycone	Catechin,epicatechin, grapefruit juice, Quercetin and kaempherol	EGCG, quercetin Kaempherol, chrysin, flavones, hesperetin,naringenin, genistein
MRPs	Flavonoid glucuronides and sulfates	Chrysin	Genistein, kaempferol, Flavopiridol, chrysin, quercetin, biochanin A, catechin, EGCG, quercetin-7-O-glucuronide
BCRP coumestrin	Flavonoid glucuronides and sulfates	Quercetin,chrysin and flavone	chrysin, biochanin A, apigenin, genistein, fisetin, kaempferol, hesperetin, naringenin, quercetin, luteolin-4-glucoside, daidzein-7-glucuronide, daidzein-4-sulfate, daidzin,ononin, genistein, sissotrin, glycitin

On the contrary, the inhibition of intestinal efflux transporters can increase drug absorption and reduce drug metabolism, thus significantly increasing drug bioavailability. Efflux transporters act as a "revolving gate" to regulate the *in vivo* bioavailability of flavonoids ((**Table 3**)). Therefore, the study of flavonoid *in vivo* treatment should not only consider the influence of a single drug metabolic enzyme or transporter, but also consider the coupling effect of enzyme-external transport on drug metabolism. At the same time, metabolic enzyme and efflux transporter coupling will further affect the drug interaction, clinical efficacy, and toxicity of flavonoids. At present, the main challenge to study the coupling of phase II drug metabolism (glucuronization/sulfation)-external transport coupling is the lack of specific transporter inhibitors. In recent years, many research groups have successfully constructed a variety of coupling models for metabolic enzyme transporter by using small interfering RNA (siRNA) or short hairpin RNA (shRNA) technology to silence metabolic enzyme and transporter genes. In conclusion, metabolic enzyme transporter coupling plays a crucial role in the treatment of flavonoids and drug interaction, which will significantly change the clinical efficacy and toxicity of the drug.

CONFLICTS OF INTEREST

The authors declare no competing financial interest.

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