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Flavonoid–drug interactions: Effects of flavonoids on ABC transporters

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Abstract

Flavonoids are present in fruits, vegetables and beverages derived from plants (tea, red wine), and in many dietary supplements or herbal remedies including Ginkgo Biloba, Soy Isoflavones, and Milk Thistle. Flavonoids have been described as health-promoting, disease-preventing dietary supplements, and a high intake of flavonoids has been associated with a reduced risk of cancer, cardiovascular diseases, osteoporosis and other age-related degenerative diseases. Due to an increased public interest in alternative medicine and disease prevention, the use of herbal preparations containing high doses of flavonoids for health maintenance has become very popular, raising the potential for interactions with conventional drug therapies. This review will summarize the current literature regarding the interactions of flavonoids with ATP-binding cassette (ABC) efflux transporters, mainly P-glycoprotein, MRP1, MRP2 and BCRP and discuss the potential consequences for flavonoid–drug transport interactions.
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Keywords: ABC proteins; P-glycoprotein; MRP; BCRP; Breast cancer resistance protein; Flavonoids; Herbal dietary supplements

Introduction

Flavonoids are a large class of naturally occurring compounds widely present in the green plant world with more than 6500 different compounds described (Harborne and Williams, 2000). In general, these compounds possess a skeleton of a chromane ring with an additional aromatic ring attached at position 2, 3 or 4 (Fig. 1). Based on different substitution and the oxidation status of ring C, flavonoids can be classified into several subclasses including flavones, flavonols, flavonones, flavanols, isoflavones and chalcones (Fig. 1). Flavonoids are also an integral component of our common diet and they are particularly abundant in vegetables, fruits and plant-derived beverages such as wine and tea. For example, grapefruit juice has been shown to contain nearly 200–850 mg/L of total flavonoids, among which naringin is the most abundant (145–638 mg/L) (Ross et al., 2000b) while orange juice mainly contains hesperidin and its content has been shown to be 200–450 mg/L (Erlund et al., 2001; Manach et al., 2003). Soy foods are rich sources for the isoflavones genistein and daidzein and every gram of dry bean contains about 1 mg of these compounds (Reinli and Block, 1996). Green tea and red wine are rich in catechins including epicatechin, epigallocatechin, epicatechin-3-gallate and epigallocatechin-3-gallate, and the content of these compounds in green tea can be as high as 1000 mg/L (Lee et al., 1995). The daily intake of total flavonoids in the U. S. diet has been estimated to be 1 gram (Kuhnau, 1976), but it is likely that this figure may be an overestimation and the actual consumption could be substantially lower.

In nature, most flavonoids exist as glycosides, but the aglycones are generally believed to be absorbed from the gastrointestinal tract after ingestion due to their higher hydrophobicity. The glycosides undergo hydrolysis by glycosidases present in the cells of the gastrointestinal mucosa or secreted by the colonic microflora. This is consistent with the observation that the time to achieve maximum plasma concentrations after oral dosing of genistin or daidzin (glycosides of genistein and daidzein, respectively) is much longer compared to that after oral dosing of the corresponding aglycones (9 h versus 2 h), and that no detectable glycosides were found in plasma (Setchell et al., 2001). Additionally,

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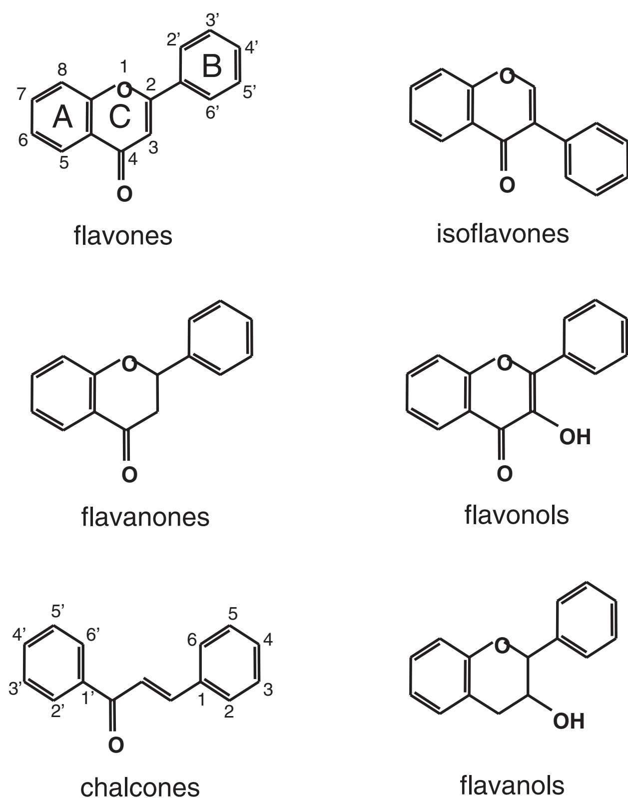

Fig. 1. The chemical structures of flavonoids.

quercetin but not quercetin glucosides could be detected in ileostomy fluids of patients after ingesting an onion meal containing 10.9 to 51.6 mg of quercetin glucosides with only a trace amount of quercetin, indicating that quercetin glucosides were efficiently hydrolyzed to the aglycone quercetin in the intestine (Walle et al., 2000). However, some controversy exists; the bioavailability of quercetin glucosides from onions was found to be significantly higher than that of the aglycone (Hollman et al., 1995, 1996), suggesting that glycosides may be also absorbed to some extent. Indeed, quercetin glucosides have been shown to be substrates of the intestinal sodium-dependent glucose transporter (SGLT-1) (Walgren et al., 2000b; Wolffram et al., 2002), implying that these glycosides could be absorbed with the help of SGLT-1. Overall, definitive information regarding flavonoid absorption and bioavailability requires further investigation. Flavonoids undergo extensive intestinal and hepatic glucuronidation and sulfation (Chen et al., 2003; Liu and Hu, 2002) and the predominant circulating chemical species in vivo after an oral dose are these conjugative metabolites. The parent compound concentrations in the systemic circulation are usually below the micromolar range, but their presence is persistent, probably due to the enterohepatic recycling of the conjugated metabolites (Setchell et al., 2001; Walle et al., 2001). However, when a large dose is given intravenously, bypassing first pass metabolism, the plasma concentrations of the parent compounds could reach more than 100 μM (Ferry et al., 1996). Flavonoid metabolism by cytochrome P450 has been observed in in vitro biotransformation studies using rat and human liver microsomes (Hu et al., 2003; Nielsen et al., 1998), but its in vivo significance is, in general, unknown.

In recent years, there has been a resurgence of scientific interest in flavonoids with more than 2000 publications per year containing “flavonoids” as a key word. This is due to the association of these compounds with a wide range of health promoting effects. Numerous studies have indicated that flavonoids have anti-oxidant, anti-carcinogenic, anti-viral, anti-inflammatory and anti-estrogenic or estrogenic activities (Havsteen, 2002; Middleton et al., 2000). High intake of flavonoids has been linked with reduced risk of cancer, cardiovascular diseases, osteoporosis and other age-related degenerative diseases (Havsteen, 2002; Hertog et al., 1993; Huxley and Neil, 2003; Keli et al., 1996; Lee et al., 1991; Middleton et al., 2000; Potter et al., 1998). For example, much of the interest in flavonoids has recently been focused on their anti-cancer properties. Epidemiological studies have suggested an association between flavonoid intake and a reduced risk of certain cancers. The lower rate of breast cancer incidence and mortality observed in Japanese women and women of Japanese origin living in Hawaii has been attributed to their high consumption of the traditional soy product-rich Japanese diet; soy products contain isoflavonoids (Messina et al., 1994). Additionally, a reduced risk of breast cancer incidence has also been associated with a high intake of daidzein and genistein in a German case-control study (Linseisen et al., 2004). In animal studies, administration of flavonoids has been shown to prevent the development and growth of various types of chemical carcinogen-induced or transplanted tumors (Buchler et al., 2003; Kohno et al., 2002; Rice et al., 2002). The proposed mechanisms for these cancer prevention effects are multifaceted, including their anti-oxidant activities, their effects on signal transduction pathways involved in cell proliferation and angiogenesis, as well as their modulation of aromatase activity, a key enzyme involved in estrogen biosynthesis, and the enzymes required for metabolic activation of procarcinogens and the detoxification of carcinogens (Kellis and Vickery, 1984; Middleton et al., 2000)}. In fact, synthetic flavonoid derivatives, flavone acetic acid and flavopiridol, have been evaluated in Phase II clinical trials for their anti-cancer activities (Aklilu et al., 2003; Siegenthaler et al., 1992). In addition to their variety of health-promoting activities, flavonoids themselves are believed to have no or little toxicity and have a long history of human consumption (Middleton et al., 2000). Very large doses of these compounds (up to 500 mg/kg) have been administered to animals, with little or no toxicity reported.

Due to their wide range of health-beneficial activities and their remarkable safety records, numerous herbal preparations containing either flavonoid glycosides or aglycones, including the widely used milk thistle (*Silybum marianus*) and red clover (*trifolium pratense*) extracts, are now marketed in various formulations as dietary supplements. The intake of flavonoids after taking these herbal products is likely very high. For example, the recommended dose of chrysin supplements is 1–4 capsules daily and each capsule contains 500 mg chrysin (http://www.herbsmd.com/shop/xq/asp/pid.1646/qx/productdetail.asp); the recommended dose of quercetin supplements is one capsule

(620 mg quercetin) daily (http://www.viable-herbal.com/singles/herbs/s914.htm). Daflon 500 is a phlebotonic drug and a vascular protecting agent containing 450 mg diosmin and 50 mg hesperidin per tablet; the suggested dose is up to 6 tablets a day (http://www.medmart.worldmedic.com/Domestic/Memberphar/servier/daflon500.htm) Therefore, the flavonoid concentration, at least in the intestine, could be very high after ingestion of some food and especially, flavonoid-containing supplements, suggesting a potential for drug interactions. Moreover, due to an increased public interest in alternative medicine and disease prevention, the use of herbal preparations for health maintenance has become more popular, and it has been estimated that herbal products are ingested by about 10% or more of the general population and 30–70% of individuals with specific disease states (Duggan et al., 2001; Ni et al., 2002). Thus, the consumption of large doses of flavonoids is frequent, increasing the risk of flavonoid–mediated pharmacokinetic interactions with conventional medication. This concern is relevant, because increasing evidence has indicated that significant or even life-threatening interactions between flavonoid-containing products and conventional drugs can occur. For example, coadministration of grapefruit juice, which contains a large amount of the flavonoid naringin, significantly increased the oral bioavailability of felodipine (Bailey et al., 1993), nimodipine (Fuhr et al., 1998), cyclosporine (Ducharme et al., 1995) and saquinavir (Kupferschmidt et al., 1998), and decreased the oral bioavailability of fexofenadine (Dresser et al., 2002) in human subjects. Silymarin has been reported to increase the clearance of metronidazole and its major metabolite, hydroxy-metronidazole (Rajnarayana et al., 2004). In animals, naringin increases the oral bioavailability of quinine in rats (Zhang et al., 2000) while baicalin and its aglycone baicalein both increase the oral bioavailability of cyclosporine in rats (Lai et al., 2004) and flavone and quercetin can increase the oral bioavailability of paclitaxel in rats (Choi et al., 2004a,b). On the contrary, quercetin and phellamurin decrease the oral bioavailability of cyclosporine in pigs and/or rats (Chen et al., 2002; Hsiu et al., 2002). Considering this accumulating evidence for flavonoid–drug interactions from clinical and animal studies, the frequent presence of high flavonoid content in dietary supplements, and the increasing popularity of many flavonoid-containing herbal products, which do not require FDA approval in the U.S. for marketing, a careful evaluation of the interaction of commonly ingested flavonoids with molecular mechanisms determining drug disposition including absorption, distribution, metabolism and elimination becomes important.

Xenobiotic and endobiotic agents must pass through various biological membrane systems for their absorption, distribution, metabolism and elimination, as well as for binding to their intracelullar targets such as enzymes or receptors to exert their biological functions. The biological membrane system is a lipid bilayer system embedded with numerous proteins including many transporters. Thus, the activities of these transporters are expected to be important determinants for the pharmacokinetics and pharmacodynamics of many important drugs especially those hydrophilic compounds. Knowledge about these transporters has been gained over the past decade, including their functional characteristics, substrate specificities, and their specialized tissue distribution and subcellular localization. Transport proteins play a key role in determining drug absorption, elimination as well as drug entry into some pharmacologically important compartments, such as brain. Therefore, understanding the interaction of flavonoids with these drug transporters will help us understand and predict potential flavonoid–drug interactions. Among these transporters, a group of so called ABC (ATP-binding cassette) transporters including P-glycoprotein, multidrug resistance associated proteins (MRPs) and breast cancer resistance protein (BCRP), have attracted special attention because of their involvement in developing multidrug resistance (MDR) (Litman et al., 2001) and their demonstrated significance in pharmacokinetics and pharmacodynamics. P-glycoprotein, MRPs and BCRP are all plasma membrane efflux transporters, pumping their substrates out of the cells using the energy derived from ATP hydrolysis (Litman et al., 2001). The focus of this overview is to summarize the current findings about the interactions of flavonoids with these efflux transporters, mainly P-glycoprotein, MRP1, MRP2 and BCRP and discuss the potential consequences for flavonoid–drug interactions.

Flavonoid–P-Glycoprotein (ABCB1) interactions

P-glycoprotein is an efflux transporter discovered by Juliano and Ling (1976). The gene-encoding P-glycoprotein consists of two members (MDR1 and MDR3) in humans, and three members (*mdr1a*, *mdr1b and mdr2*) in rodents (Chen et al., 1986; Croop et al., 1989; Gros et al., 1988; Lincke et al., 1991). Only human MDR1 and its mouse orthologue *mdr1a* and *mdr1b* proteins have drug transport capabilities. Human MDR3 and mouse *mdr2* proteins are mainly located in the liver canalicular membranes and are believed to function as phosphatidylcholine translocases or flippases (Ruetz and Gros, 1994; Smit et al., 1994a,b; 1993). The molecular structure of P-glycoprotein has been proposed to consist of two homologous segments, each consisting of six transmembrane domains, and a nucleotide-binding domain with ATPase activity. The ATPase activity can hydrolyze ATP and provide the energy for transporting substrates against a concentration gradient (Ambudkar et al., 1992; Germann, 1996). P-glycoprotein has a very broad spectrum of substrates including many anti-cancer agents (e.g., anthracyclines, vinca alkaloids, epipodophyllotoxins and taxol) (Gottesman and Pastan, 1993), cardiac drugs (e.g., digoxin, quinidine) (Schinkel et al., 1995; Tsuruo et al., 1984), HIV protease inhibitors (e.g., saquinavir, indinavir, ritonavir) (Lee et al., 1998), immunosuppressants (e.g., cyclosporine) (Meador et al., 1987), antibiotics (e.g., actinomycin D) (Horio et al., 1989), steroids (e.g. cortisol, aldosterone, dexamethasone) (Ueda et al., 1992; van Kalken et al., 1993) and cytokines (e.g., IL2, IL-4, IFN-γ) (Drach et al., 1996). The only common characteristics shared by these substrates are that most of these compounds are hydrophobic, positively charged or neutral compounds with a planar structure (Gottesman and Pastan, 1993; Kusuhara et al., 1998); however, negatively charged compounds, such as methotrexate and

phenytoin, have also been reported as P-glycoprotein substrates (de Graaf et al., 1996; Norris et al., 1996; Potschka and Loscher, 2001). P-glycoprotein is frequently detected in various resistant human tumors and often predicts poor prognosis (Chan et al., 1991; Dalton, 1994; Gregorcyk et al., 1996; Koh et al., 1992; List, 1996; Marie et al., 1991; Nooter and Sonneveld, 1994; van der Zee et al., 1995; Zochbauer et al., 1994). Thus, P-glycoprotein is believed to be one of the major mechanisms for MDR and represents a pharmacological target for reversing MDR. In addition to its tumor expression, high levels of P-glycoprotein expression have also been detected at the apical membranes of epithelial cells in the excretory organs such as intestine, liver and kidney, and the luminal side of endothelial cells in the blood brain barrier (Cordon-Cardo et al., 1989; Thiebaut et al., 1987; Thiebaut et al., 1989). This polarized expression suggests that P-glycoprotein would limit the oral bioavailability and brain distribution, and facilitate both biliary excretion and renal elimination of its substrate drugs. This has been demonstrated in a variety of clinical and animal studies, especially those using P-glycoprotein knockout animals (Schinkel et al., 1997, 1994, 1995; Sparreboom et al., 1997). For example, the *mdr1a* (−/−) mice have been shown to be 50 to 100-fold more sensitive to the central nervous system toxicity of ivermectin, with a 90-fold increase in the brain accumulation of this drug in comparison to the wild type controls (Schinkel et al., 1994), clearly demonstrating that P-glycoprotein is an essential component of the blood brain barrier controlling the entry of xenobiotics into the brain. The plasma concentration–time curve (AUC) of paclitaxel, a typical P-glycoprotein substrate, has also been shown to be 2- and 6-fold higher in *mdr1a* (−/−) knockout mice than in the wild type mice after i.v. and oral administration, respectively (Sparreboom et al., 1997), suggesting the important role of this transporter in drug absorption and elimination.

A number of studies have investigated the interactions of flavonoids with P-glycoprotein-mediated transport, and the flavonols kaempferol, galangin and quercetin, were first reported to potently stimulate P-glycoprotein-mediated transport of 7,12-dimethylbenz(*a*)anthracene, a carcinogen known to induce mammary tumors in animals, in drug resistant MCF-7 cells selected with adriamycin (Phang et al., 1993). This stimulatory effect was also observed for P-glycoprotein-mediated transport of anti-cancer drug adriamycin in HCT-15 colon carcinoma cells (Critchfield et al., 1994). However, opposite observations were reported by other investigators. Scambia et al. (1994) observed a dose-dependent inhibitory activity of quercetin for the P-glycoprotein-mediated transport of adriamycin. This inhibitory activity of quercetin was also demonstrated for P-glycoprotein-mediated transport of Hoechst 33342 using purified and reconstituted P-glycoproteins (Shapiro and Ling, 1997a). The explanation for these controversial observations is largely unknown. It has been proposed that P-glycoprotein possesses at least two positively cooperative sites for drug binding, with the H site preferring Hoechst 33342 to rhodamine 123 and the R site preferring rodamine 123 to Hoechst 33342. Binding to one of these sites has been shown to stimulate the binding to the other site and transport activity (Shapiro and Ling, 1997b). It has been suggested that quercetin could preferentially bind to the H site, since it inhibited the transport of Hoechst 33342 while it stimulated the transport of rhodamine 123 (Shapiro and Ling, 1997b). Therefore, the controversial reports regarding flavonoid–P-glycoprotein interactions might be explained by the different binding properties of the model substrates used in the study, since binding of quercetin to the H site will presumably inhibit the transport of the substrates binding to the H site while stimulating the transport of substrates binding to the R site. However, opposite effects on P-glycoprotein-mediated transport have also been observed when the same model substrate was used (Critchfield et al., 1994; Scambia et al., 1994), thus other factors responsible for these inconsistent observations need to be identified. Mitsunaga et al. (2000) demonstrated that quercetin and kaempferol, at 10 μM, decreased, while, at 50 μM, increased the steady-state accumulation of vincristine in the mouse brain capillary endothelial cells (MBEC4 cells) expressing P-glycoprotein; similar biphasic effects were also obtained in vivo, and the brain-to-plasma concentration ratio of vincristine in mice was shown to be significantly decreased by the co-administration of 0.1 mg/kg of quercetin, but increased by 1 mg/kg of quercetin (Mitsunaga et al., 2000). The mechanism for this biphasic effect was believed to be that low concentrations of quercetin indirectly stimulate P-glycoprotein by increasing P-glycoprotein phosphorylation; however, high concentrations of quercetin inhibit, instead of phosphorylating P-glycoprotein (Mitsunaga et al., 2000). Despite these earlier controversial observations, the majority of the more recent studies have indicated that many flavonoid aglycones have an inhibitory activity on P-glycoprotein-mediated transport. These flavonoids include genistein, biochanin A, morin, phloretin, silymarin, chrysin, flavone, hesperetin, naringenin, 3,3′,4′,5,6,7,8-heptamethoxyflavone, nobiletin, tangeretin and the green tea polyphenols epicatechin gallate, catechin gallate and epigallocatechin gallate (Castro and Altenberg, 1997; Jodoin et al., 2002; Mitsunaga et al., 2000; Zhang and Morris, 2003). The interaction of flavonoid glycosides such as naringin, hesperidin and rutin with P-glycoprotein appears to be small (Mitsunaga et al., 2000). The mechanism(s) underlying this flavonoid–P-glycoprotein interaction(s) is not clear, but may involve their direct binding to multiple binding sites of P-glycoprotein. It has been shown that flavonoids genistein, epicatechin gallate, catechin gallate, epigallocatechin gallate and silymarin can inhibit the labeling of P-glycoprotein with its photoactive substrates (Castro and Altenberg, 1997; Jodoin et al., 2002; Zhang and Morris, 2003), indicating these flavonoids may directly bind to the P-glycoprotein substrate binding site. In addition, flavonoids have also been shown to directly bind to the purified recombinant C-terminal nucleotide-binding domain from mouse P-glycoprotein (NBD2), and the binding domain may overlap the ATP binding site and vicinal steroid binding site (Conseil et al., 1998). Different flavonoids may also interact with P-glycoprotein differently, since opposite effects on P-glycoprotein ATPase activity have been observed for different flavonoids (Zhang and Morris, 2003). The structural activity relationship for flavonoid–P-glycoprotein

interaction has also been extensively studied mainly by evaluating the binding affinity of different flavonoids with mouse NBD2 and reviewed by Boumendjel et al. (2002). In general, the presence of the 5-hydroxyl group, the 3-hydroxyl group and the 2,3-double bond appears to be important for potent flavonoid–NBD2 interaction. In addition, isoflavonoids with ring B branched at position 3 instead of 2 have lower P-glycoprotein interaction activity (Boumendjel et al., 2002). The concentrations required for flavonoids to produce a significant modulation of P-glycoprotein activity seem to be, in general, 10 μM or higher, but could be achievable in the intestine after ingestion of food and, especially, dietary supplementation. For example, grapefruit juice contains 145–638 mg/L naringin (Ross et al., 2000b), equivalent to 250–1100 μM, and orange juice contains 200–450 mg/L hesperidin (Erlund et al., 2001; Manach et al., 2003), equivalent to 330–740 μM. Although these flavonoid glycosides may not potently interact with P-glycoprotein, their corresponding aglycones released from these glycosides in the intestine could be present in high enough concentrations to inhibit intestinal P-glycoprotein, resulting in drug interactions. The concentration of flavonoid aglycones in the systemic circulation may not be high enough for significant P-glycoprotein interaction, except for the more potent flavonoids. In addition, the main metabolites of flavonoids (glucuronides and sulfate conjugates) may not interact with P-glycoprotein because these metabolites are organic anions. So, systemic inhibition of P-glycoprotein by flavonoids or their metabolites may be, in general, insignificant after regular supplementation; however, interaction could occur after administration of an extremely high dose, especially by i.v. injection.

The pharmacokinetic interactions of flavonoids with P-glycoprotein substrates have been demonstrated by several animal studies. For example, co-administration of quercetin and moxidectin subcutaneously increased moxidectin bioavailability in lambs (Dupuy et al., 2003); naringin can increase the oral bioavailability of quinine in rats (Zhang et al., 2000); baicalein and its aglycone baicalein can both increase the oral bioavailability of cyclosporine in rats (Lai et al., 2004); flavone and quercetin can increase the oral bioavailability of paclitaxel in rats (Choi et al., 2004a,b) and quercetin can increase oral bioavailability of digoxin in pigs (Fig. 2) and resulted in a very serious toxicity (Wang et al., 2004). All these studies indicated that flavonoid–P-glycoprotein interactions could occur in vivo, resulting in pharmacokinetic interactions. However, because most of these P-glycoprotein substrate drugs are also CYP3A substrates and flavonoids can also inhibit CYP3A, separation of the flavonoid effects on CYP3A and P-glycoprotein activity in the above-mentioned studies is difficult. Thus the observed interaction could be due to flavonoid–P-glycoprotein interaction, flavonoid–CYP3A interaction or both. Modulation of P-glycoprotein by flavonoids has also been indicated in several clinical drug interactions. For example, grapefruit juice, which contains a large amount of flavonoids, has been shown to increase the oral bioavailability of felodipine, nimodipine, cyclosporin and saquinavir (Bailey et al., 1993; Ducharme et al., 1995; Fuhr et al., 1998; Kupferschmidt et al., 1998); all these drugs are both P-glycoprotein and CYP3A4 substrates,

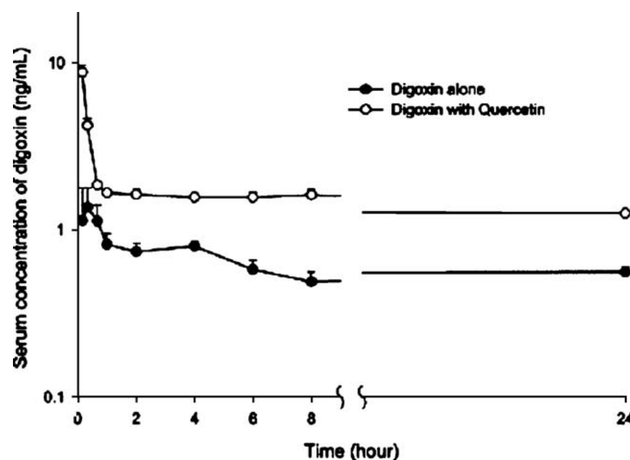

Fig. 2. Mean (±S.E.) serum concentration–time profiles of digoxin after oral administration of digoxin (0.02 mg/kg) alone (●) and co-administration with quercetin (oral, 40 mg/kg) (○) in four male Yorkshire pigs. Reproduced with permission from Wang et al. (2004), with permission from Elsevier.

indicating that inhibition of P-glycoprotein by flavonoids may contribute, at least partly, to the pharmacokinetic interaction. However, due to the complex mix of ingredients present in grape fruit juice and their modulation of CYP3A4, an unequivocal role of flavonoid modulation of P-glycoprotein in these interactions can not be demonstrated.

Flavonoid–MRP1 (ABCC1) interactions

MRP1 is a 190-KD membrane transporter cloned in 1992 (Cole et al., 1992). It is the first member of multidrug resistance associated proteins family that currently consists of nine members. The molecular structure of MRP1 consists a N-terminal segment of five transmembrane domains linked to a typical ABC protein "core" structure with twelve transmembrane domains and two ATP binding sites (Borst et al., 1999; Leslie et al., 2001a). In contrast to P-glycoprotein, which mainly transports hydrophobic organic cations, MRP1 is an organic anion transporter and transports anionic conjugates of lipophilic compounds including glutathione, glucuronide and sulfate conjugates (Konig et al., 1999) out of cells, using the energy derived from ATP hydrolysis. Some amphiphilic cations or neutral compounds, such as anti-cancer agents anthracyclines, etoposide and vinca alkaloids can also be transported by MRP1 (Cole et al., 1994; Grant et al., 1994; Kruh et al., 1994; Zaman et al., 1994) using glutathione (GSH) as a co-transporting factor (Evers et al., 2000; Loe et al., 1996, 1998; Renes et al., 1999). MRP1 expression has been detected in a number of human tumors and might represent a mechanism of clinical cancer MDR (Filipits et al., 1996; Ito et al., 1998; Laupeze et al., 2002; Nooter et al., 1997; Oshika et al., 1998; Ota et al., 1995; Sugawara et al., 1995; Tada et al., 2002; Young et al., 1999). In addition, MRP1 is distributed in a wide range of tissues throughout the body (Borst et al., 1999, 2000), and in polarized epithelial cells, it is mainly confined to the basolateral membranes (Borst et al., 1999, 2000; Evers et al., 1996). In contrast to P-glycoprotein, the expression of MRP1 in the

intestine and hepatocytes is limited and its contribution to oral bioavailability and biliary excretion is unclear. However, its wide tissue distribution indicates that MRP1 may limit the distribution of its substrates into various tissues and in this way, serve a protective function in tissues (Leslie et al., 2001a). Indeed, mice without functional Mrp1 demonstrated increased bone barrow toxicity to the cytotoxic agents etoposide and vincristine (Johnson et al., 2001; Lorico et al., 1997; Wijnholds et al., 1997). MRP1 was also shown to be expressed in the basolateral membrane of the choroid plexus epithelium (Rao et al., 1999), and may contribute to the blood-CSF (cerebrospinal fluid) barrier function, preventing the entry of amphiphilic anions or anti-cancer drug substrates into CSF (Wijnholds et al., 2000).

The interaction of flavonoids with MRP1 was first reported by Versantvoort et al. (1994, 1993)), who demonstrated that the flavonoids genistein, biochanin A, apigenin and quercetin may inhibit MRP1-mediated transport. Genistein was also proposed as a probe compound for discriminating P-glycoprotein and non-P-glycoprotein mediated MDR based on its inability to inhibit P-glycoprotein when used below 200 μM (Versantvoort et al., 1994, 1993). Since then, a number of studies revealed that many other flavonoid aglycones including morin, chalcone, silymarin, phloretin, chrysin, kaempferol, naringenin, myricetin, galangin, baicalein, luteolin, robinetin, diosmetin, chrysoeriol, tamarixetin and isorhamnetin can all inhibit MRP1-mediated transport to a varying degree (Leslie et al., 2001b; Nguyen et al., 2003; van Zanden et al., 2005). The IC_{50} values of many of these compounds for MRP1 inhibition have been shown to be below 50 μM, with several potent ones such as diosmetin, chrysoeriol and tamarixetin below 10 μM (van Zanden et al., 2005). Flavonoid glycosides such as genistin and naringin have been shown to have much lower MRP1 inhibition activity (Leslie et al., 2001b). The MRP1 inhibition activity observed in these studies was most likely mediated by the parent compounds since MRP1 inhibition by some of the flavonoids including genistein, naringenin, apigenin, quercetin and myricetin has also been demonstrated in membrane vesicle studies as well, where conjugation of these compounds should not occur (Leslie et al., 2001b). The mechanism(s) for flavonoid–MRP1 interactions may involve the binding to the nucleotide binding domains, and/or the substrate binding site(s) (Leslie et al., 2001b; Trompier et al., 2003). Some flavonoids, such as quercetin, myricetin, apigenin and naringenin, have been shown to stimulate GSH transport by MRP1 (Leslie et al., 2003, 2001b); therefore, depletion of cellular GSH, a cofactor for MRP1-mediated transport of chemotherapeutic agents, could also represent a potential mechanism for MRP1 inhibition by these compounds. Indeed, pre-incubation of Panc-1 cells with a number of flavonoids resulted in decreased level of cellular GSH (Nguyen et al., 2003). The structural requirements of flavonoids for potent MRP1 inhibition have been recently investigated (van Zanden et al., 2004, 2005) and a planar structure due to the presence of a 2,3-double bond in ring C, as well as the number of methoxyl and hydroxyl groups appear to be important (van Zanden et al., 2004, 2005). Potential in vivo drug interactions due to flavonoid inhibition of MRP1 is currently unclear. The IC_{50} concentrations of many flavonoids could be easily achievable in the intestine after regular food intake or dietary supplementation; however, MRP1 expression in the intestine is limited and its contribution to drug oral bioavailability is not known. The systemic concentrations of parent compound after regular flavonoid ingestion may not reach the micromolar range (Setchell et al., 2001; Walle et al., 2001), so systemic inhibition of MRP1 by unchanged flavonoids might be insignificant after regular supplementation. However, because flavonoid glucuronides and sulfate conjugates should represent good MRP1 substrates, and are present at relatively high concentrations after flavonoid intake, these flavonoid conjugates may also inhibit MRP1, and thus altered distribution of MRP1 substrates following ingestion of high dose of flavonoids is possible.

Flavonoid–MRP2 (ABCC2) interactions

MRP2 (cMOAT) is another member of the multidrug resistance associated protein family, sharing a 49% amino acid identity with MRP1 (Leslie et al., 2001a). The molecular structure of MRP2 is very similar to that of MRP1, possessing an extra N-terminal segment of five transmembrane domains linked to a typical ABC protein structure of twelve transmembrane domains and two nucleotide binding domains (Leslie et al., 2001a). This transporter shares a similar but not an identical substrate spectrum with MRP1, and the transport efficiency for any common substrate can differ substantially from each other (Konig et al., 1999). MRP2 expression has also been shown to confer MDR to several anti-cancer agents in vitro (Cui et al., 1999), but its clinical significance is unknown. In contrast to MRP1, MRP2 has a more restricted expression pattern in normal tissues. MRP2 is mainly localized to the apical membrane of polarized cells such as hepatocytes, intestinal epithelial cells and renal proximal tubule cells (Buchler et al., 1996; Konig et al., 1999; Schaub et al., 1999), and therefore, it is expected to limit oral bioavailability and facilitate biliary and renal excretion of its substrates. The loss of MRP2 in humans is associated with Dubin–Johnson syndrome, characterized by impaired biliary excretion of bilirubin glucuronides and other anionic conjugates (Kajihara et al., 1998; Kartenbeck et al., 1996; Paulusma et al., 1997; Toh et al., 1999). MRP2 has also been shown to be present in the luminal surface of brain capillary endothelium in rats and pigs (Miller et al., 2000), and contributes to the barrier function of the blood brain barrier (Potschka et al., 2003).

Although, MRP2 and MRP1 have similar molecular structures and substrate spectra, the structural requirements of flavonoids for MRP2 inhibition appear to be different from that for MRP1 inhibition, since many fewer flavonoids have been shown to be potent inhibitors of MRP2. Quercetin, at a 50 μM concentration, inhibited MRP1-mediated transport of dinitrophenyl glucuronide (DNP-SG) in MRP1-transfected MDCKII cells to an extent similar to the typical MRP1 inhibitor, MK571; however, similar inhibition was not obtained for MRP2-mediated DNP-SG transport in MRP2-transfected MDCKII cells (van Zanden et al., 2004). A recent study published by the

same group (van Zanden et al., 2005) which evaluated the inhibitory activity of 29 flavonoid compounds, belonging to the subclasses of flavones and flavonones, against MRP1- and MRP2-mediated calcein efflux in MDCKII cells transfected with these transporters, demonstrated that only two flavonoids (myricetin and robinetin) inhibited MRP2 with IC_{50} values below 50 μM, albeit fifteen compounds can inhibit MRP1 with IC_{50} values below 50 μM (Table 1) (van Zanden et al., 2005). The mechanisms for flavonoid–MRP2 interaction has not been extensively studied, but may be similar to that for flavonoid–MRP1 interaction, including the binding to nucleotide binding domains and/or the substrate binding site(s). Several studies have shown that flavonoids and flavonoid glycosides may be transported by MRP2, although with a low affinity (Vaidyanathan and Walle, 2001, 2003; Walgren et al., 2000a; Walle and Walle, 2003; Walle et al., 1999a), consistent with their binding to the substrate binding site(s). The IC_{50} values of robinetin and myricetin for MRP2 inhibition were shown to be around 20 μM (van Zanden et al., 2005); dietary supplements containing 100 mg myricetin and 100 mg robinetin per tablet are now commercially available, and consumption of one tablet would result in a maximal intestinal concentration greater than 200 μM, assuming an intestinal fluid volume of 1.65 liter (Davies and Morris, 1993). Therefore, supplementation of these flavonoids might be expected to increase the bioavailability of MRP2 substrate drugs. In addition, the conjugative metabolites of flavonoids, glucuronides and sulfate conjugates are MRP2 substrates (Walle et al., 1999b). Since these conjugated flavonoids can reach a high concentration in the systemic circulation after supplementation, they could possibly inhibit MRP2, resulting in decreased biliary, or renal excretion of MRP2 substrates. In fact, inhibition of MRP2-mediated biliary excretion of conjugated bilirubin by the synthetic flavonoid flavopiridol and/or its conjugates is believed to be responsible for flavopiridol treatment-induced conjugative hyperbilirubinemia observed in patients (Jager et al., 2003).

Table 1
The percentage inhibition of MRP1 and MRP2 mediated transport of calcein by flavonoids (25 μM) and the determined IC_{50} values for MRP1 and MRP2 inhibition

	MRP1		MRP2	
	Inhibition at 25 μM (%)	IC50 (μM)	Inhibition at 25 μM (%)	IC50 (μM)
Flavone	36	>50	5	>50
3-Hydroxyflavone	3	>50	2	>50
3′-Hydroxyflavone	13	>50	0	>50
4′-Hydroxyflavone	15	>50	1	>50
Chrysin	10	>50	2	>50
3,3′-Dihydroxyflavone	4	>50	1	>50
3′,4′-Dihydroxyflavone	57	24.4±4.1	16	>50
Galangin	43	35.3±7.3	0	>50
Baicalein	48	30.9±4.4	28	>50
Apigenin	47	35.1±9.6	2	>50
Naringenin	2	>50	0	>50
3,3′,4′-Trihydroxyflavone	26	>50	17	>50
Kaempferol	72	19.4±3.6	2	>50
Fisetin	2	>50	1	>50
Luteolin	53	22.4±4.8	17	>50
Eriodictyol	31	>50	13	>50
Morin	30	49.0±7.6	8	>50
Quercetin	63	21.8±3.5	5	>50
Taxifolin	8	>50	3	>50
Catechin	15	>50	0	>50
Robinetin	75	13.6±3.9	76	15.0±3.5
Myricetin	63	20.2±4.3	68	22.2±3.9
Acacetin	18	>50	1	>50
Kaempferide	40	>50	2	>50
5,7,3′,4′-Tetramethoxyflavone	76	7.9±1.5	20	>50
Diosmetin	84	2.7±0.6	17	>50
Chrysoeriol	85	4.0±0.7	31	>50
Tamarixetin	68	7.4±3.4	8	>50
Isorhamnetin	60	14.3±2.8	10	>50

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Flavonoid–BCRP (ABCG2) interactions

BCRP is a recently cloned plasma membrane efflux transporter (Allikmets et al., 1998; Doyle et al., 1998; Miyake et al., 1999) which is also known as ABCP (ABC transporter in placenta) and MXR (Allikmets et al., 1998; Miyake et al., 1999). Human BCRP consists of 655 amino acids with a molecular weight of 72.1 KD (Doyle et al., 1998). Because this transporter has only six transmembrane domains and one N-terminal ATP binding domain (Allikmets et al., 1998), in contrast to a “core” structure of twelve transmembrane domains and two ATP binding sites of P-glycoprotein and other typical ABC proteins, BCRP is considered a half ABC transporter and its transport function may require the formation of a homodimer (Litman et al., 2001). The BCRP substrates include anti-cancer agents such as epipodophyllotoxins (e.g., etoposide, teniposide), camptothecins or their active metabolites (e.g., topotecan, SN-38, 9-aminocamptothecin, CPT11), mitoxantrone, bisantrene, methotrexate, flavopiridol and HIV-1 nucleoside reverse transcriptase inhibitors (e.g., zidovudine, lamivudine). The well-known P-glycoprotein substrates vincristine and paclitaxel do not appear to be BCRP substrates (Allen et al., 1999; Allen and Schinkel, 2002; Doyle et al., 1998; Kawabata et al., 2001; Robey et al., 2001; Schellens et al., 2000; Volk et al., 2002; Wang et al., 2003). Interestingly, some sulfate conjugates and glucuronides have recently been shown to be transported by BCRP (Suzuki et al., 2003). Significant BCRP expression has been detected in some human tumors (Faneyte et al., 2002; Kanzaki et al., 2001; Ross et al., 2000a; Sargent et al., 2001; Sauerbrey et al., 2002; Steinbach et al., 2002; van der Kolk et al., 2002) and its potential association with MDR has also been reported (Friedrich et al., 2004; Steinbach et al., 2002). The normal tissue distribution and subcellular localization of BCRP is similar to that of P-glycoprotein, and high levels of BCRP expression have been detected in the human placenta syncytiotrophoblast plasma membrane, liver canalicular membrane, intestinal apical membrane, and the luminal surface of brain capillaries (Cooray et al., 2002; Maliepaard et al., 2001; Zhang et al., 2003). The important role of BCRP in limiting the oral bioavailability and distribution into placenta, and facilitating biliary excretion of its substrates has been convincingly

demonstrated using Bcrp(−/−) knockout mice (Jonker et al., 2002). For example, the oral bioavailability and fetal accumulation of topotecan (a BCRP substrate) in Bcrp1(−/−) mice have been shown to be about 6- and 2-fold higher, respectively, compared with wild type animals (Jonker et al., 2002). It should be also emphasized that the expression of BCRP in the human intestine has been shown to be even greater than P-glycoprotein (Taipalensuu et al., 2001) and therefore, the contribution of BCRP to the oral bioavailability could be comparable with, if not greater than, that of P-glycoprotein. The functional role of BCRP expression at blood brain barrier in the brain uptake of BCRP substrates is not very clear but an in situ brain perfusion study comparing the brain uptake of BCRP substrates mitoxantrone and dehydroepiandrosterone sulfate in both wild type and Bcrp1 knockout mice indicated that Bcrp1 may only play a minor role in the brain uptake of these substrates (Lee et al., 2005).

Many flavonoids have been shown to interact with BCRP. In our recent study (Zhang et al., 2004b), we extensively investigated the effects of 20 dietary flavonoids (apigenin, biochanin A, chrysin, daidzein, epigallocatechin, epigallocatechin-3-gallate, fisetin, genistein, hesperetin, kaempferol, luteolin, morin, myricetin, naringenin, naringin, phloretin, phloridzin, quercetin, silybin and silymarin) on BCRP-mediated transport of mitoxantrone in BCRP-overexpressing drug resistant MCF-7 MX100 and NCI-H460 MX20 cells selected with mitoxantrone (Table 2) . The majority of these compounds, when tested at a 50 μM concentration, could significantly increase mitoxantrone accumulation in these BCRP-overexpressing cells, as did fumitremorgin C, a well-known BCRP inhibitor; there were no or minimal effects in the corresponding drug sensitive cells, indicating that these compounds inhibit BCRP-mediated efflux. Among these 20 flavonoids, four flavonoid aglycones epigallocatechin, epigallocatechin-3-gallate, morin and myricetin, and two flavonoid glycosides naringin and phloridzin, which were the only flavonoid glycosides included in the study, failed to produce a statistically significant increase of mitoxantrone accumulation in either of the drug resistant cells, suggesting that these compounds may be not BCRP inhibitors or much weaker inhibitors. The flavonoids apigenin, biochanin A, chrysin, genistein, kaempferol, hesperetin, naringenin and silymarin, which are all present in food and dietary supplements, were further tested for their effects on mitoxantrone cytotoxicity in both drug resistant MCF-7 MX100 and sensitive MCF-7/sensitive cells and all of these compounds potentiated mitoxantrone cytotoxicity in the drug resistant cells in a flavonoid concentration-dependent manner with minimal effects in the drug sensitive cells. Following a one-day co-incubation with 50 μM of these compounds (except for silymarin), the resistance of MCF-7 MX100 cells to mitoxantrone was completely reversed. The most potent compounds chrysin and biochanin A could significantly decrease mitoxantrone IC_{50} value in MCF-7 MX100 cells at a concentration as low as 2.5 μM. The potent inhibition of BCRP by flavonoids was also demonstrated by other groups (Cooray et al., 2004; Imai et al., 2004; Yoshikawa et al., 2004). For example, Imai et al. (Imai et al., 2004) demonstrated that cytotoxicity of SN-38 and mitoxantrone, which are both well-known BCRP substrates, can be substantially increased by 3 μM or 10 μM of the flavonoids genistein, naringenin, hesperetin, acacetin, apigenin, chrysin, diosmetin, luteolin, galangin, kaempferide and kaempferol in human leukemic K562 cells engineered to over-express BCRP, but not in the wild type K562 cells. The expression of BCRP was not altered by this flavonoid treatment, and so the sensitization of SN-38 and mitoxantrone by these flavonoids is most likely due to the inhibition of BCRP activity. In this study, the investigators also examined the effects of a number of flavonoid glycosides including naringenin-7-glucosides, apigenin-7-neohesperidoside (rhoifolin), diosmetin-7-β-rutinoside (diosmin), luteolin-4′-*O*-glucoside, kaempferol-3-glucoside, kaempferol-7-*O*-neohesperidoside, quercetin-3-arabioglucoside (peltatoside) and quercetin-3-rutinoside (rutin) on BCRP-mediated SN-38 resistance. Most of these flavonoid glycosides had little effect, but two glucosides naringenin-7-glucoside and luteolin-4′-*O*-glucoside moderately reversed BCRP-mediated SN-38 resistance (Imai et al., 2004). Since most of the commonly ingested flavonoids can inhibit BCRP-mediated efflux with high or considerable potency, the potential of these flavonoids for altering pharmacokinetics, especially oral bioavailability, of conventional medications, might be anticipated. The IC_{50} values of apigenin, biochanin A, chrysin,

Table 2
Effects of flavonoids on the accumulation of mitoxantrone in both parent and BCRP-overexpressing MCF-7 and NCI-H460 cells

	MCF-7/ sensitive	MCF-7 MX100	NCI-H460	NCI-H460 MX20
Control	100±13.4	100±14.8	100±4.42	100±11.0
Apigenin	88.6±9.85	321±36.1***	89.0±10.8	355±36.2***
Biochanin A	114±12.4	440±99.5***	129±14.2***	463±59.7***
Chalcone	108±32.6	495±140***	126±16.0*	531±72.0***
Chrysin	98.5±8.03	389±94.1***	97.4±15.0	367±35.5***
Daidzein	106±10.9	215±13.1***	93.8±18.3	297±23.1***
EGC	101±10.6	155±19.1	73.5±11.9*	95.6±15.0
EGCG	52.9±8.78***	132±15.6	25.7±2.92***	34.4±8.00
Fisetin	105±16.1	223±33.2***	78.4±10.0	226±37.0***
Genistein	104±12.9	412±47.0***	105±10.1	331±54.0***
Hesperetin	112±15.9	362±55.2***	101±26.8	305±55.8***
Kaempferol	85.2±11.3	378±17.3***	80.5±10.4	301±42.5***
Luteolin	69.5±10.2***	155±19.5	63.7±8.48***	213±23.6***
Morin	60.2±9.25***	186±33.8	45.8±6.92***	153±30.3
Myricetin	86.5±11.8	102±17.5	52.0±5.40***	75.2±16.3
Naringenin	109±11.8	345±46.4***	102±17.05	338±28.0***
Naringin	107±6.09	149±62.1	98.7±6.66	102±23.2
Phloretin	94.8±6.84	216±44.1***	96.9±12.3	304±33.9***
Phloridzin	97.7±11.7	114±14.6	95.2±12.5	78.0±14.3
Quercetin	80.3±8.64	206±18.3*	71.6±5.52***	233±18.4***
Silibin	105±18.5	209±19.7*	128±13.6***	331±41.4***
Silymarin	103±11.9	302±60.9***	104±18.4	344±70.7***
FTC	116±9.30	439±89.8***	124±19.8*	404±40.4***

*$p<0.05$; **$p<0.01$; ***$p<0.001$. The cellular accumulation of mitoxantrone in the BCRP-overexpressing MCF-7 MX100 and NCI-H460 MX20 cells, as well as their corresponding parental cells was determined in the absence or presence of flavonoids (50 μM). FTC (10 μM) was used as a positive control. The accumulation of mitoxantrone was expressed as percent of control (in the presence of the vehicle, 0.1% DMSO). Reproduced with permission from Zhang et al. (2004b).

genistein, kaempferol, hesperetin, naringenin and silymarin for BCRP inhibition, as determined by their ability to increase mitoxantrone accumulation in MCF-7 MX100 cells, have been shown to range from 0.39 μM for chrysin to 33 μM for silymarin (Zhang et al., 2004a). These concentrations should be easily achievable in the intestine after ingestion of certain foods or dietary products. In addition, apigenin, biochanin A, chrysin, genistein, kaempferol, hesperetin, naringenin and silymarin have been shown to inhibit BCRP additively when equal molar concentrations of these compounds were used in combination (Zhang et al., 2004a); evaluation of the potential for flavonoid–drug interactions needs to consider the combined effects of multiple flavonoids, as well as the combined effects of flavonoids with other food components such as organic isothiocyanates (Ji and Morris, 2004), which can also inhibit BCRP and are present in food and dietary supplements. We have found (Zhang et al., 2005a) that the important structural features for flavonoid–BCRP interaction are similar but not identical to those shown to be important for the interaction of flavonoids with the C-terminal nucleotide binding domain (NBD2) of mouse P-glycoprotein (Boumendjel et al., 2001, 2002; Conseil et al., 1998); the presence of a 2,3-double bond in ring C, ring B branched at position 2, hydroxylation at position 5 and lack of hydroxylation at position 3 all appear to be important for potent BCRP inhibition. The similar structural requirements for flavonoid–BCRP interaction and flavonoid–NBD2 (P-glycoprotein) interactions suggest that flavonoid inhibition of BCRP may involve their interaction with the BCRP nucleotide binding domain; however, interaction with the BCRP substrate binding site(s) is also a possible mechanism because many flavonoids can stimulate BCRP ATPase activity as seen for the typical BCRP substrate mitoxantrone (Cooray et al., 2004). The inhibition of BCRP by flavonoids is most likely mediated by the parent compounds instead of their metabolites such as glucuronides and sulfate conjugates, since flavonoids without any hydroxyl substitutions such as flavone, flavonone and 7,8-benzoflavone, which can not be conjugated, are potent BCRP inhibitors (unpublished data from this laboratory), and genistein was shown to be transported by BCRP in its unchanged form (Imai et al., 2004). The interaction of flavonoid glucuronides and sulfate conjugates with BCRP may be important, although this has not been investigated. These conjugative metabolites represent the predominant species in the systemic circulation after flavonoid intake (Setchell et al., 2001; Walle et al., 2001). It has been shown that estrogen sulfate conjugates are BCRP substrates (Imai et al., 2003). Since flavonoids share considerable structural similarity with estrogens, flavonoid sulfate conjugates are therefore also likely to be BCRP substrates. If this is to be true, flavonoid sulfate conjugates may competitively inhibit BCRP-mediated transport and result in pharmacokinetic interactions.

The in vivo effects of these flavonoid–BCRP interactions have not been extensively studied. In our recent report (Zhang et al., 2005b), co-administration of chrysin and 7,8-benzoflavone, which have been shown to be very potent BCRP inhibitors with IC_{50} values below 1 μM, at doses up to 50 mg/kg with topotecan (oral dosing) failed to produce a significant increase of topotecan oral bioavailability in rats and/or mdr1a/1b(−/−) knockout mice, while the typical BCRP and P-glycoprotein inhibitor GF120918 increased topotecan bioavailability. This lack of in vitro–in vivo association is somehow surprising, considering the strong potency of these compounds for inhibiting BCRP. The actual reason(s) for this in vitro–in vivo discrepancy is unclear, but the species-dependent nature of this flavonoid–BCRP interaction may represent one of the possible explanations (Zhang et al., 2005b). More studies on the potential species differences in flavonoid–BCRP interaction are needed in order to correctly interpret the animal data and to evaluate the clinical potential for flavonoid–drug interactions.

Conclusion

In conclusion, many flavonoids have been shown to interaction with the efflux transporters especially P-glycoprotein and BCRP in in vitro studies, and the potential consequences for flavonoid–drug interactions due to flavonoid modulation of these efflux transporters have been reported. However, the significance of these flavonoid–efflux transporter interactions in pharmacokinetic interactions has not been unequivocally demonstrated. Since the involvement of other drug transporters and metabolizing enzymes in the disposition of substrates can confound the interpretation of in vivo studies, more specific substrates are needed to clearly address this issue. In addition, although flavonoid glucuronides and sulfate conjugates are expected to be the predominant circulating chemical species, studies have not investigated their interaction with these efflux transporters. In addition, since flavonoids are usually ingested on a chronic basis, their long term effects on the expression of these efflux transporter needs to be investigated and may be of importance regarding flavonoid–drug interactions.

Note-added-in-proof

The findings of a recent study suggest that quercetin glucuronides represent BCRP substrates (Sesink, A.L., Arts, I. C., de Boer, V.C., Breedveld, P., Schellens, J.H., Hollman, P.C., Russel, F.G., 2005. Breast cancer resistance protein (Bcrp1/Abcg2) limits net intestinal uptake of quercetin in rats by facilitating apical efflux of glucuronides. Mol. Pharmacol. Jun;67(6):1999–2006.

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