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Oral Bioavailability and Disposition of Phytochemicals

Yan Li and James W. Paxton
Department of Pharmacology & Clinical Pharmacology, School of Medical Sciences, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand

1. Introduction

Higher plants produce a vast variety of secondary metabolites known as phytochemicals (PCs) which appear to protect the plant against a variety of stresses such as UV irradiation, pathogenic attacks, and perhaps even consumption by herbivores. Many of these non-nutrient PCs have been shown to exert a wide range of biological effects, and epidemiological and nutritional studies have identified a protective role for PCs in the prevention of cancer, diabetes, cardiovascular and neurodegenerative diseases (Kris-Etherton et al., 2002; Aruoma et al., 2003; Surh, 2003; Balunas & Kinghorn, 2005; Duthie, 2007; Espin et al., 2007; Russo, 2007; Dembinska-Kiec et al., 2008; Hooper et al., 2008; Khan et al., 2008). Unlike some cytotoxic chemicals derived from natural products (e.g., etoposide, daunorubicin and paclitaxel), PCs are found in high concentrations in fruits, vegetables, nuts, wine and tea, and intake can be up to several hundred milligrams per day (Manach et al., 2005). PCs which have been associated with health benefits, include glucosinolates, organic isothiocyanates, dibenzocyclooctadienes, sulphur-containing compounds of alliaceae, terpenoids (carotenoids, monoterpenes, and phytosterols), flavonoids and polyphenols (e.g., anthocyanins, flavones, flavan-3-ols, isoflavones, stilbenoids, and ellagic acid) (Balunas & Kinghorn, 2005; Espin et al., 2007). Bioavailability and tissue distribution of these PCs in humans are key factors that need to be clearly established in association with their biological effects. Recently various drug metabolizing enzymes and drug transporters such as the ATP binding cassette (ABC) and the solute carrier (SLC) transporters have been cloned and functional analyses suggest that they play significant roles in the absorption and disposition of most drugs and PCs (Zhang et al., 1998; Zhang & Benet, 2001; Borst & Elferink, 2002; Faber et al., 2003; Sarkadi et al., 2006; Shitara et al., 2006; Hu et al., 2003; Zhou et al., 2004; Morris & Zhang, 2006; Zhang et al., 2007; Shukla et al., 2008; Zhang et al., 2009). They are present in all tissues and play pivotal roles in the defense of the body against amphipathic carcinogens and toxins. Many drug metabolizing enzymes and transporters are under tight transcriptional regulation by nuclear receptors, suggesting their functions are subject to environmental and dietary influences (Borst & Elferink, 2002; Petri et al., 2003; Lancon et al., 2007; Giacomini et al., 2010). In addition, PCs may modulate the expression and function of drug metabolizing enzymes and drug transporters which govern xenobiotic bioavailability (Wang & Morris, 2007; Kim et al., 2009; Shukla et al., 2009). This review will highlight the various barriers to dietary phytochemicals, approaches for assessing these interactions, and their implications in pharmacokinetics and potential clinical applications.

2. Absorption from gastrointestinal (GI) tract

To achieve their beneficial effects, other than on the GI tract itself, these PC molecules must be delivered to target tissues and organs after overcoming several absorption barriers in the GI tract (Figure 1). Firstly, they must dissolve in the fluids of the GI tract and survive the different pH environment ranges from extreme low in the stomach to slightly basic in some segments of the small intestine. They may also be subjected to degradation and metabolism by intestinal enzymes, such as the glycosidases, esterases, oxidases and hydrolases, originating both from the host and the myriad of microbiota that inhabit the GI tract (Sousa et al., 2008). Actually the large intestine accommodates most of the GI microbiota and the rate and extent of metabolism by bacteria will be influenced by the amount of the PC that reaches the distal gut. Many plant flavonoids exist in the *O*-glycoside form within the plant and undergo rapid GI hydrolysis to remove the glucose conjugates and form their respective aglycons (Crespy et al., 2002; Walle et al., 2005). The latter are more lipophilic and and thus are more efficiently absorbed across the GI wall than the parent glycoside, providing they are not subject to intestinal transporter-mediated absorption. However, interactions with intestinal ABC and SLC transporters may cause unpredictable absorption kinetics of many PCs which cannot be simply predicted from their physicochemical properties. Transporter-related absorption phenomena, such as the limited and nonlinear intestinal permeability and absorption of PCs, may lead to extensive variability in their oral bioavailability, resulting in low plasma concentrations and lack of pharmacological effect on the one hand, or elevated concentrations and toxicity on the other.

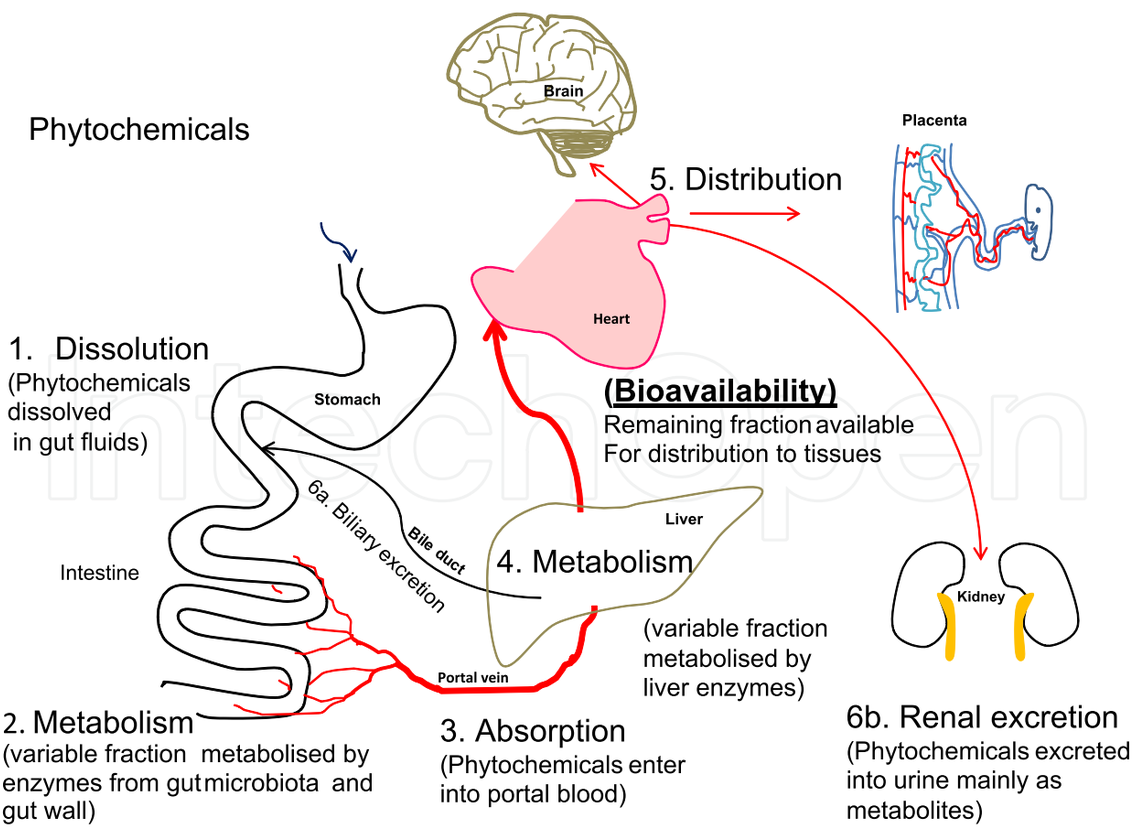

Fig. 1. Absorption and disposition of phytochemicals in humans.

The human family of ABC transporters contains 49 members with 7 subfamilies including several important xenobiotic transporters, such as P-glycoprotein (P-gp, ABCB1), multidrug resistance protein 1-9 (MRP 1-9, ABCC1-6 and ABCC10-12, respectively) and breast cancer resistance protein (BCRP, ABCG2) (Borst & Elferink, 2002). They actively transport chemically diverse substrates including amino acids, lipids, inorganic ions, peptides, saccharides, metals, xenobiotics, and proteins out of cells. In most examples of primary active transport that have been observed, transport of the substrates against their concentration and chemical potential gradients was driven by the hydrolysis of ATP (Higgins, 1992). To date, important SLC transporters involved in xenobiotic absorption and disposition mainly include organic cation transporter (OCT) and organic anion transporter (OAT); and organic anion transporting polypeptide (OATP) families.

Many ABC and SLC transporters have been identified in the GI tract including OATPs, P-gp, MRPs and BCRP on the apical membrane and OCT1 and MRP 3, 4, 5 on the basolateral (blood) side (Figure 2). PCs can act as substrates for ABC transporters (Table 1), which can severely limit their bioavailability. The expression of BCRP transcripts in human jejunum are higher than that of P-gp (Taipalensuu et al., 2001; Maliepaard et al., 2001), suggesting that BCRP may play an important role in limiting the intestinal absorption of its substrates. Knocking out mouse Bcrp led to significant increases in the oral bioavailability of daidzen (3.7-fold) and genistein (1.8-fold) compared to wild type mice (Enokizono et al., 2007). Several flavonoids such as quercetin, kaempferol, and diverse anthocyanins and anthocyanidins commonly found in grapes and berries, malvidin, petunidin, malvidin-3-galactoside, malvidin-3,5-diglucoside, cyanidin-3-galactoside, peonidin-3-glucoside and cyanidin-3-glucoside have also been identified as BCRP substrates (Dreiseitel et al., 2009; An et al., 2010). Thus BCRP may limit the absorption of these PCs, but to date, human pharmacokinetic data are not available to confirm this.

Accumulating evidence, mainly from *in vitro* studies has indicated that many flavonoid aglycones and anthocyanins and anthocyanidins are P-gp and BCRP inhibitors, including genistein, biochanin A, quercetin, morin, phloretin, silymarin (a mixture of silibinins,

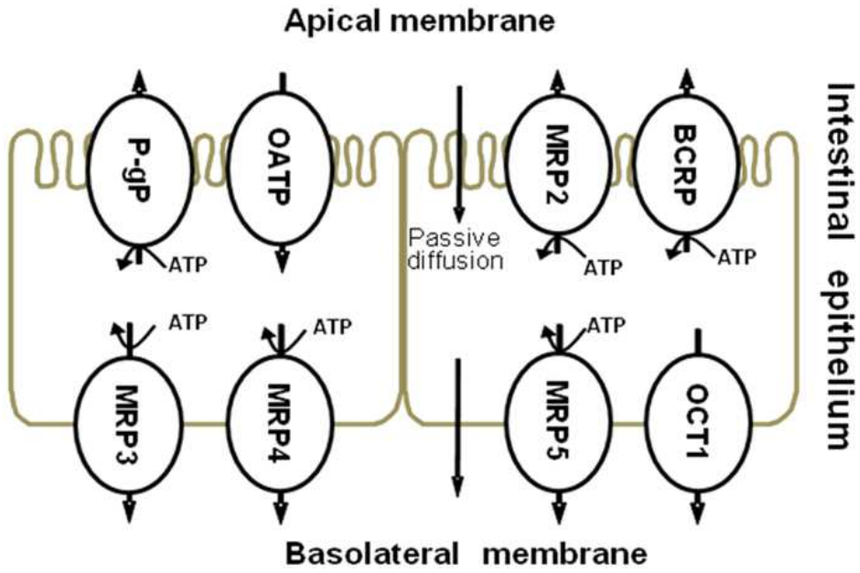

Fig. 2. Localization of ABC and SLC transporters in human small intestine.

Name	Symbol	Tissue location	PC substrates	PC inhibitors	References
P-gp	ABCB1 MDR1	Liver, intestine, brain	Quercetin, EGCG, Biochanin A	Genistein, naringenin, hesperetin, acacetin, apigenin, chrysin.	(Jodoin et al., 2002; Wang et al., 2002; Zhang & Morris, 2003; de Castro et al., 2007; Taur & Rodriguez-Proteau, 2008)
MRP1	ABCC1	All major tissues	(-)-Epicatechin-3-gallate	Quercetin, Naringenin, Kaempferol, Apigenin, Genistein Schisandrin A and B, Schisandrol A and B	(Versantvoort et al., 1993; Versantvoort et al., 1994; Versantvoort et al., 1996)
MRP2	ABCC2,	Liver, kidney, intestine, brain	(-)-Epicatechin-3-gallate, 4-O-methyl-EGCG	Myricetin, robinetin	(Borst et al., 1999; Zhou et al., 2008)
MRP3	ABCC3	Small intestine, pancreas, colon, placenta, adrenal gland	Baicalein-7-glucuronide,	?	(Borst et al., 1999; Zhou et al., 2008)
MRP4	ABCC4	Kidney	?	Quercetin, silymarin	(Borst et al., 1999; Zhou et al., 2008b ;Wu, 2005)
MRP5	ABCC5	Most tissues	?	Quercetin, silymarin	(Borst et al., 1999; Zhou et al., 2008b ;Wu, 2005)
BCRP	ABCG2	Placenta, liver, the small intestine, colon, lung, kidney	Quercetin, genistein, resveratrol, malvidin, petunidin, malvidin-3-galactoside, malvidin-3,5-diglucoside, cyanidin-3-galactoside, peonidin-3-glucoside and cyanidin-3-glucoside	Genistein, naringenin, hesperetin, acacetin, apigenin, chrysin, diosmetin, luteolin, galangin, kaempferide, kaempferol, cyanidin, peonidin, cyaniding-3,5-diglucoside, malvidin, pelargonidin, delphinidin, petunidin, delphinidin-3-glucoside, cyaniding-3-rutinoside, malvidin-3-glucoside, pelargonidin-3,5-diglucoside, malvidin-3-galactoside, cannabinoids	(Litman et al., 2001; Holland et al., 2007; de Wolf et al., 2008; Dreiseitel et al., 2009)

Table 1. An overview of tissue distribution, substrates and inhibitors of P-gp, MRPs and BCRP.

isosilyin A and B, silychristin A and B, and silydianin), chrysin, hesperetin, naringenin, and the green tea polyphenols, epicatechin gallate, catechin gallate and epigallocatechin gallate (Table 1) (Castro & Altenberg, 1997; Jodoin et al., 2002; Wang et al., 2002; Zhang & Morris, 2003; de Castro et al., 2007; Taur & Rodriguez-Proteau, 2008; Dreiseitel et al., 2009). It has been suggested that such inhibitory PCs could be used to reverse the ABC transporter-based constraints on the GI absorption of other substrate PCs and that this may represent a useful strategy for improving their bioavailability. For example, the oral bioavailability of biochanin A was increased approximately 2-fold when coadministered with the BCRP inhibitors quercetin and epigallocatechin-3-gallate (EGCG) in rats (Moon & Morris, 2007). However this effect may at least partially be due to inhibition of metabolizing enzymes, as there is evidence that both quercetin and the green tea polyphenols may inhibit both Phase 1 and 2 metabolism (Cermak & Wolffram, 2006). Kaempferol has also been reported to increase quercetin permeability across MDCKII-Bcrp monolayers by inhibition of Bcrp-mediated quercetin efflux (An et al., 2010). Recently it has also been suggested that intestinal ABC transporters may function as barriers to absorption of PCs (e.g., resveratrol, green tea catechins and flavonoids) by cooperating with intestinal Phase 2 metabolizing enzymes (Zhang et al., 2004; Ebert et al., 2005; Zhang et al., 2007; Juan et al., 2010), implying a joint role in limiting oral absortption of PCs. In an *in situ* intestine perfusion model in Mrp2-deficient rats, Bcrp was shown to limit net intestinal absorption of quercetin by pumping quercetin glucuronides back into the lumen (Sesink et al., 2005).

Several uptake transporters, such as organic anion transporting polypeptide (OATP) and organic cation transporter (OCT) from the SLC transporter superfamily are also functionally expressed on human intestine tissues (Figure 2) (Hagenbuch & Meier, 2003; Giacomini et al., 2010), and have recently been associated with the oral absorption of some PCs. For example, quercetin was absorbed by passive diffusion and a pH-dependent mechanism mediated by OATP in a Caco-2 cell monolayer model (Nait Chabane et al., 2009). As quercetin is also a substrate for the efflux transporters P-gp and BCRP, a balance between these counteracting transporters may allow a more precise control of the cellular accumulation of such substrate compounds, but the actual biological implication of this fine-tuning mechanism remains unclear at the moment. This transport process may be further complicated in that many PCs present in plants are linked to sugar moieties, which may have an impact on their oral absorption. For example, there is *in vitro* and *in silico* evidence that the human glucose transporter 1 (SLC2A1) and rat glucose transporter 4 (slc2a4) transports quercetin (Strobel et al., 2005; Cunningham et al., 2006). In addition, the pig but not human sodium-dependent glucose transporter-1 (SGLT1) appeared to be involved in the intestinal uptake of quercetin glucosides (Cermak et al., 2004; Kottra & Daniel, 2007).

3. Metabolism (enterocytes & hepatocytes)

Possibly of greater importance as a defensive barrier against these invading foreign molecules is the battery of both Phase 1 and Phase 2 enzymes present in the enterocytes (Figure 3). The Phase 1 reactions include oxidation, reduction and hydrolysis, which primarily serve to increase the hydrophilicity of the molecule, and expose or add a functional group (such as a hydroxyl group) to facilitate Phase 2 conjugation reactions. Oxidation is the most predominant reaction involved in the Phase 1 metabolism of xenobiotics, and is principally carried out by a family of closely related isozymes known as

the cytochrome P450-dependent mixed-function oxidases (CYPs). In humans, CYP1A, CYP2C, CYP2D and CYP3A are responsible for metabolising the bulk of xenobiotics that enter the body via the oral route (Lewis & Ito, 2008). CYP3A4/5 with its broad substrate specificity is particularly important in xenobiotic metabolism, making up 70 and 30% of total CYPs in the intestines and liver, respectively (Zhang & Benet, 2001).

The parent PCs (or their Phase 1 metabolites) that contain suitable functional groups (e.g., a hydroxyl group) often undergo conjugation reactions with endogenous compounds to yield more polar and water soluble compounds. The latter are usually ideal substrates for active transport out of the cell, and eventually excretion from the body. The principal conjugation reaction is the formation of β-glucuronides catalysed by a family of enzymes known as the uridine diphosphoglucuronosyl transferases (UGTs), but conjugation with a sulpho moiety (SO_3^-) or glutathione also occurs, catalysed by various sulphotransferases (SULTs) and glutathione-S-transferases (GSTs), respectively. Less polar conjugates may also be formed by methylation, catalysed by catechol-O-methyl transferase (COMT). These Phase 2 conjugation reactions are particularly important for PCs such as epi-gallocatechin-3-gallate (EGCG), which is the most abundant catechin in green tea. EGCG has numerous hydroxyl groups and undergoes extensive Phase 2 metabolism, including glucuronidation, sulphation, and methylation (Lambert et al., 2007; Yang et al., 2007). Several recent studies using liquid chromatography-tandem mass spectrometry (LC-MS/MS) have demonstrated

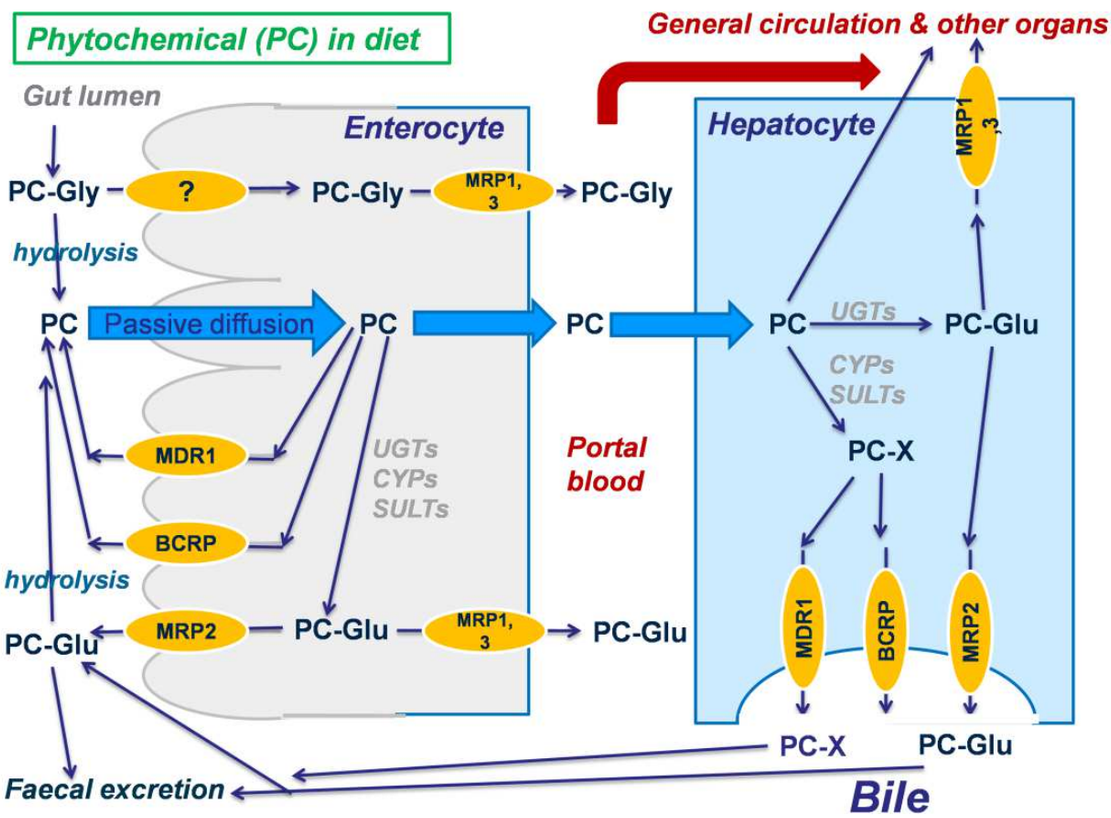

Fig. 3. Metabolism and disposition of phytochemicals (PC) and their metabolites in enterocytes and hepatocytes. PC-Gly, glycoside phytochemical; PC-Glu, glucuronide conjugate; PC-X, phytochemical metabolite

that after ingestion of some flavonoids, Phase 2 conjugates of the aglycon such as glucuronides, sulphates and methylated metabolites predominate in the blood circulation, rather than the original plant glycoside or aglycon (Janisch et al., 2004; Zhang et al., 2007). The extent to which these metabolites contribute to the overall beneficial effects of PCs in the body is largely unknown, and needs further investigation. Most evidence for drugs has indicated that their Phase 2 conjugates have little pharmacological activity but exceptions certainly exist, such as morphine-6-glucuronide and ezetimibe-glucuronide which appear to have greater pharmacological activity than their parent compound (Lotsch & Geisslinger, 2001; Kosoglou et al., 2005). In studies with green tea polyphenols, the metabolites mostly had reduced biological activity, but in some systems the metabolites had the equivalent or greater activity than the parent PC (Lambert et al., 2007). Other *in vitro* studies have shown that phloridzin-glucuronide is significantly more potent at protecting human SH-SY5Y neuroblastoma cells from hydrogen peroxide-mediated cell death than the parent molecule phloridzin (Stevenson et al., 2008), and that quercetin-3-glucuronide was significantly more potent than quercetin in a model of inflammation using human neutrophils (Suri et al., 2008). There is also evidence that the position of the glucuronide conjugate on the flavonoid can influence its biological activity (Day et al., 2000; O'Leary et al., 2003). Certainly these conjugated metabolic products are ideal substrates for various active transmembrane transport processes, in particular the excretory processes of the liver and kidney.

Although the Phase 1 and 2 metabolic enzymes are found in the epithelial cells of the gut wall, by far the greatest concentrations are found in the liver (Figure 3), where they form a major barrier to the further distribution of the parent PC to other organs, such as of the heart, kidney, lungs and brain. The liver's location and the portal venous blood supply from the intestines make it well suited for the protection of the body from possible toxic xenobiotics contained in our diet. During this first passage through the liver, many PCs will undergo substantial extraction and metabolism (known as first-pass metabolism). The resulting metabolic products are then exported back out of the liver into the blood stream and carried to the kidney where they may be excreted in the urine. Alternatively, metabolites such as glucuronide conjugates may be exported in the bile and released into the gut lumen. Thereafter, the metabolite conjugate may be excreted in the faeces, or alternatively it may be further metabolised by gut microbial enzymes, such as β-glucuronidase, which has the ability to cleave off the glucuronide and reform the less-polar aglycon, which may then be reabsorbed. This cycle is known as enterohepatic recirculation and may result in a longer exposure of the body to the PC. Evidence for such enterohepatic recirculation has been obtained for the flavonoid baicalein 7-*O*-glucuronide with a rat model (Xing et al., 2005), but whether a similar process occurs for some PCs in humans is not known.

4. Distribution

Presumably, if the PC overcomes the defence mechanisms of the gut and the liver, it will enter the systemic circulation and be distributed in the bloodstream to the other major organs of the body and possible site(s) of action. In pharmacology, the term bioavailability is used to indicate the relative amount of the ingested parent xenobiotic that reaches the main cardiovascular circulation. Bioavailability is usually measured by taking peripheral blood samples over a period of time after ingestion and analysing for xenobiotic concentration. It is assumed that this blood concentration is an acceptable index for the concentration or

exposure at the site of action. Most PCs can pass with ease through the pores of the capillaries of organs such as the heart and lungs, but not some pharmacological sanctuaries, such as the brain, testis, fetus and stem cells. The tissue distribution of xenobiotics is significantly influenced by ABC transporters as the latter contribute to the maintenance of these pharmacological sanctuaries (Borst & Elferink, 2002; Huls et al., 2009; Mruk et al., 2011). For many PCs present in the bloodstream either as parent compound or metabolite, active efflux by ABC transporters may represent a major rate-limiting factor in their distribution or access to these sanctuaries. Phytochemical interactions with these efflux transporters could result in either: a further decrease in substrate PC distribution to the site, if the transporters were stimulated or induced; or accumulation of substrate, if the transporters were inhibited. The brain capillaries are surrounded with a protective cellular sheath of glial cells (the so-called blood brain barrier, BBB) resulting in permeability characteristics more closely resembling those of tightly bound tissue cell walls (Pardridge, 1993). To gain access to the brain, a PC must be highly lipid-soluble, or subject to uptake transport processes. MDR1, BCRP, MRP1, MRP3, MRP4 and MRP5 genes were shown by qRT-PCR to be expressed in the BBB (Dauchy et al., 2009). P-gp, BCRP and MRP1 have been located at the apical membrane of brain endothelial cells (Figure 4) (Kubota et al., 2006; Dauchy et al., 2009), and there is evidence that P-gp limits the penetration of various drugs across the BBB (Linnet & Ejsing, 2008). However the effects of several potent PC inhibitors of P-gp on passage across the BBB appeared to be minor (Tsai et al., 2001). Similarly, the uptake of the BCRP substrates, mitoxantrone and dehydroepiandrosterone sulfate, into the brain did not vary significantly between wild type and Bcrp knockout mice (Lee et al., 2005). In contrast, significant increases in the brain concentrations of various phytoestrogens including genistein (9.2-fold), daidzen (5.6-fold) and coumestrol (3.9-fold) were reported in Bcrp knockout mice compared to wild type (Enokizono et al., 2007). Similar results were also observed in the testis, suggesting that Bcrp may play a protective role reducing the accumulation of such compounds in both the brain and the testis. Likewise in a rat

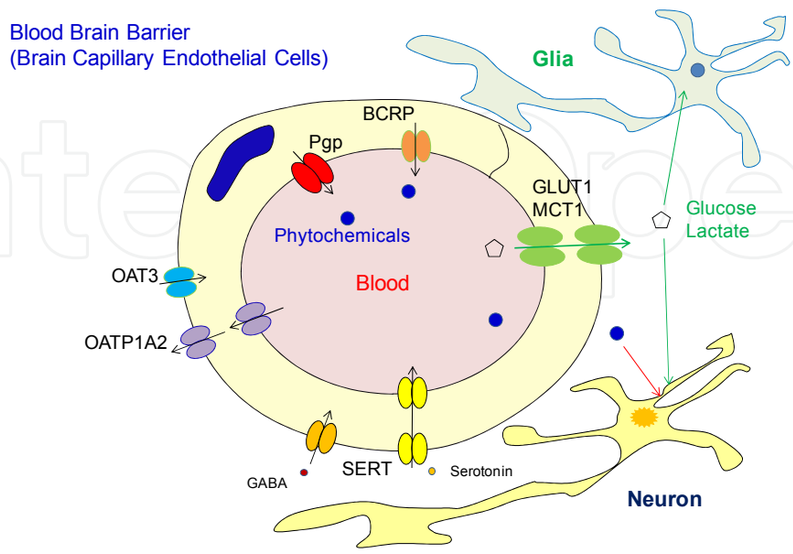

Fig. 4. Localization of ABC and SLC transporters in human BBB. GLUT1, glucose transporter 1; MCT1, monocarboxylate transporter 1; SERT, serotonin transporter

hemisphere perfusion study, the brain accumulation of quercetin was dramatically increased by pretreatment with GF120918 (a P-gp and BCRP inhibitor), but not with PSC833 (a P-gp inhibitor) (Youdim et al., 2004). A recent study using the *ex vivo* rat BBB model indicated that curcumin inhibited BCRP activity at nanomolar concentrations and significantly increased the penetration of sulfasalazine across the BBB (Shukla et al., 2009). However, due to the low oral bioavailability of curcumin, such concentrations are rarely achieved with low to sub nanomolar concentrations typically being observed in plasma, even after oral dosing at 8 g/day for 18 months (Dhillon et al., 2008). BCRP is most abundantly expressed in the apical membrane of placental syncytiotrophoblasts, suggesting that it may play a role in protecting the fetus by impeding xenobiotic penetration across the placental barrier (Jonker et al., 2000; Evseenko et al., 2006). It has been shown that genistein accumulates in Bcrp knockout mice fetuses when genistein was included in the diet of pregnant mice during gestation (Enokizono et al., 2007), implying the involvement of Bcrp in genistein efflux in mouse placenta. However, a recent study shows that genistein at low, environmentally relevant concentration (10 ng/mL) can transfer across the human placenta at term at a extent similar to antipyrine (a well-known passive diffusion marker) in a placenta perfusion system (Balakrishnan et al., 2010), which suggests human BCRP may play a minor role in limiting the fetal exposure to genistein. These discrepancies may be due to species differences or differences between *in vivo* and ex *vivo* experimental systems. Since fetal exposure to genistein may have adverse consequences with regard to the development of the fetus (North & Golding, 2000), the regulatory role of BCRP in genistein transfer in term placenta needs further studies. As many flavanoids present in diet are potent modulators of BCRP and dietary flavonoids are in greater use, their influence on fetal exposure to various PC substrates of BCRP may also require further studies.

5. Excretion

The ABC and SLC transporters are abundantly expressed in the liver and kidney and regulate the excretion of many compounds, including PCs and their metabolites. In the liver, OAT2, OCT1 and OATPs are located in the sinusoid membrane to extract xenobiotics from blood; while BCRP, P-gp and MRP2 are found in the hepatocyte canalicular membrane effluxing compounds into the bile (Hooivelda & van Montfoorta, 2000). The inhibition of these transporters in hepatocytes can increase the concentrations of PC substrates in the bloodstream and/or decrease their biliary excretion and prolong their stay in the body. For example, biliary excretion of glucuronide and sulfate conjugates of silymarin flavonolignans was reduced by approximately 96 and 78%, respectively, in Mrp2-deficient Wistar rats, compared to wildtype (Miranda et al., 2008). Since biliary excretion of glucuronide and sulfate conjugates is the major route for silymarin's elimination in humans and rodents (Miranda et al., 2008), the pharmacokinetics of silymarin may be susceptible to MRP2 inhibition/induction or to pathological conditions where MRP2 may be deficient, such as in cholestatic liver disease or in Dubin-Johnson Syndrome (Keitel et al., 2000; Borst & Elferink, 2002). In contrast, MRP1 and 3 are found at the sinusoid membrane effluxing substrates back into the bloodstream, but are expressed at low levels under normal conditions (Ros et al., 2003). However in situations where MRP2 may be deficient, MRP3 may be upregulated, apparently to compensate for the diminished ability to excrete organic acids into bile (Keitel et al., 2000). Chronic administration of PCs however, may result in the upregulation of transporters via activation of the pregnane X receptor (PXR) or the aryl hydrocarbon

receptor (AhR) in hepatocytes, lessening the effects of inhibition (Lim & Lim, 2006; Zhang et al., 2007; Zhang et al., 2009).

In the kidneys, P-gp, MRP2, MRP4 and BCRP are expressed in the apical membranes and OCT2, OATs and OATP4C1 in the basolateral side of the cells lining the proximal tubules, transporting xenobiotics out of the blood into the urine (Ichikawa et al., 1991; van Aubel et al., 2002; Leslie et al., 2005; Huls et al., 2008; Giacomini et al., 2010). MRP2, 4 and BCRP efflux anionic or conjugated compounds (e.g., Phase 2 metabolites of some flavanoids), while more hydrophobic compounds are extruded by P-gp. As many PCs are excreted as conjugated metabolites by the kidney, there exists the possibility of competitive inhibition of these transport processes with drugs whose major route of elimination is by the kidney. It would appear cautionary to monitor plasma concentrations for drugs with a narrow therapeutic index in patients who are also consuming large amounts of PCs, perhaps as herbal medications or health supplements.

6. Modulation of bioavailability by PCs

There is accumulating evidence that PCs are able to modulate the activity of some ABC and SLC transporters by numerous mechanisms, resulting in significant changes in the oral bioavailability of substrate xenobiotics. For example, 1-hour pretreatment of mice with oral curcumin (400 mg/kg) resulted in a 13-fold increase in the bioavailability (as measured by the area under the plasma concentration-time curve (AUC)) of the Bcrp substrate sulfasalazine (anti-inflammatory drug) (Shukla et al., 2009). Although inhibition of sulfasalazine's metabolism could not be ruled out, it was believed that direct competitive inhibition of Bcrp was the major mechanism involved. In contrast, more prolonged treatment of rats with a lower dose of oral curcumin (60 mg/kg for 4 days) produced a down regulation in P-gp concentrations (> 50% reduction) in the gut, leading to a 1.6-fold increase in the AUC of the β-blocking drug, celiprolol (Zhang et al., 2007). The latter does not undergo metabolism and is a P-gp substrate, and thus the reduction in P-gp in the gut was deemed responsible for the increased bioavailability of celiprolol. It was also intriguing to note that the effect of curcumin was tissue specific, resulting in a greater than 2-fold P-gp increase in the liver but no effect in the kidney. Most studies of PC-transporter interactions have been undertaken using *in vitro* systems (Table 2) or *in vivo* animal studies and the difficulty in extrapolating to humans is apparent. Recently Molnar *et al.* (2006) have demonstarated that a wide range of lipophilic PCs (diterpenes, triterpines and carotenoids) were able to inhibit human P-gp *in vitro* at the low μg/ml range, whereas other combinations had positive synergistic activity (Molnar et al., 2006). Using purified PCs on P-gp over-expressing cells *in vitro*, Patel *et al.* (2004) showed that quercetin, hypericin and kaempferol were able to increase the cellular uptake of ritonavir by 5- to 8-fold (Patel et al., 2004). It is also interesting to note that *in vitro* assays or short-term exposure to these polyphenols *in vivo* appears to inhibit the action of efflux pumps and increase substrate bioavailability, whilst chronic exposure in healthy volunteers actually increases the expression of P-gp. For example, extracts from St John's Wort (SJW) have been shown to up-regulate the expression of intestinal P-gp (Durr et al., 2000; Hennessy et al., 2002), that may subsequently reduce the bioavailability of substrates, such as the antiviral drugs indinavir and saquinavir that are used in the treatment of acquired immune deficiency syndrome (AIDS) (Perloff et al., 2001). Treatment with SJW is able to reduce plasma concentrations of

these drugs by up to 57% in healthy human volunteers, potentially leading to sub-therapeutic levels (Piscitelli et al., 2000). Hyperforin has been identified as the most likely candidate causing this inducing effect by binding and subsequent activation of PXR leading to increased expression not only of P-gp but also various Phase 1 and 2 metabolizing enzymes (Moore et al., 2000). In fact, the induction of CYPs and UGTs is probably the more important mechanism causing the majority of the many clinically significant drug interactions with SJW that have been reported (Hennessy et al., 2002).

Quercetin has been identified as a P-gp substrate and inhibitor, and has been reported to cause a 55 % increase in oral bioavailability of fexofenadine in healthy volunteers (Kim et al., 2009). Fexofenadine is non-sedating antihistamine which is a P-gp substrate that undergoes negligible metabolism in humans. Interestingly the oral bioavailability of fexofenadine is significantly decreased when taken with grapefruit juice (GFJ) or one of its major PC components, naringin (Bailey et al., 2007). The mechanism responsible is thought to be

	P-gp	BCRP	MRP1	MRP2	MRP4	MRP5	References
Phytochemicals							
Apigenin	**?**	**I**	**I**	**I**	**?**	**?**	(Versantvoort et al., 1994; Imai et al., 2004)
Biochanin A	**I^{ca}**	**I^{ca}**	**I^{ca}**	**?**	**?**	**?**	(Versantvoort et al., 1993; Zhang & Morris, 2003; Zhang et al., 2004)
Curcumin	**I**	**I**	**I**	**?**	**?**	I	(Anuchapreeda et al., 2002; Chearwae et al., 2006; Shukla et al., 2009; Li et al., 2010)
Cyanidin	**I**	**I**	**?**	**?**	**?**	**?**	(Dreiseitel et al., 2009)
Daidzein	**?**	**I^{ca}**	**I**	**?**	**?**	**?**	(Versantvoort et al., 1994; Imai et al., 2004)
EGCG	**×**	**?**	**S**	**S**	**?**	**?**	(Jodoin et al., 2002; Hong et al., 2003)
Epicatechin	**?**	**?**	**S**	**S**	**?**	**?**	(Hong et al., 2003)
Genistein	**I^{ca}**	**S^{ca}, I^{ca}**	**I**	**S**	**?**	**?**	(Imai et al., 2004)
Narigenin	**S, I**	**I**	**I**	**S**	**?**	**I**	(Imai et al., 2004)
Naringin	**I^{ca}**	**I**	**?**	**?**	**?**	**?**	(Imai et al., 2004)
Puerarin	**?**	**?**	**?**	**?**	**?**	**?**	(Imai et al., 2004)
Quercetin	**S, I**	**I**	**I**	**S, I**	**I**	**I**	(Wu et al., 2005)
Resveratrol	**I**	**I**	**I**	**?**	**I**	**×**	(Nabekura et al., 2005; Wu et al., 2005; Breedveld et al., 2007)
Silymarin	**I^{ca}**	**I**	**I**	**?**	**I**	**I**	(Zhang & Morris, 2003; Cooray et al., 2004; Wu et al., 2005)

Table 2. Phytochemical substrates and inhibitors of P-gp, MRPs and BCRP. I, inhibitor; S, Substrate; Ca, Experiments carried only in cancer cells; ×, not a substrate or inhibitor; ? Not determined.

inbition of OATP1A2 which is involved in intestinal uptake of fexofenadine, and naringin (and hesperidin, also found in GFJ) have been identified as potent inhibitors of this transporter. This is an uncharacteristic interaction with GFJ as most reported interactions have involved markedly increased drug bioavailability, often resulting in significant toxicity (Bailey et al., 1991). Further studies have indicated that the main mechanism was inhibition of intestinal CYP3A4 by the furanocoumarins in GFJ, including bergamottin and 6′,7′-hydroxybergamottin (Dahan & Altman, 2004). However these may not be the sole contributors, as other PCs found in GFJ, such as quercetin and kaempferol have also been shown to cause inhibition of the CYPs *in vitro* (Zhou et al., 2003; Dahan & Altman, 2004; Rodeiro et al., 2008). These studies serve to illustrate the potential complexity of the interactions between multiple PCs acting by different mechanisms dependent on the period of exposure to modulate uptake and efflux transporters and metabolizing enzymes in both enterocytes and hepatocytes.

7. Improving the bioavailability of PCs

Although many PCs have postulated health benefits, most appear to suffer from poor oral bioavailability which makes their utility as such agents rather tenuous. The biological activity of many of these PCs have been amply demonstrated *in vitro* but the effects *in vivo* are much more limited, probably due to the sub-micromolar concentrations achieved in plasma after ingestion (Baur & Sinclair, 2006; Moon & Morris, 2007; Zhang et al., 2007) (Anand et al., 2007). Apart from modulating ABC transporter function, PCs can also act as substrates for these efflux pumps, which can severely limit their bioavailability. For example, quercetin has very limited bioavailability through gut epithelia and regardless of the amount consumed orally, plasma concentrations of quercetin rarely exceed 1 μM. Although not specifically proven, this is likely to be at least in part due to BCRP expression in gut epithelia (see (Murakami & Takano, 2008) for review). Curcumin has well demonstrated antitumour activity *in vitro* and is currently in clinical trials for the treatment of various cancers but with limited success (Dhillon et al., 2008; Hatcher et al., 2008). However, the poor absorption and rapid first-pass metabolism resulting in poor oral bioavailability and low systemic concentrations, continue to be a major problem with curcumin's use in the clinic and appear to be responsible for the disconnect between curcumin's *in vitro vs in vivo* biological activity (Anand et al., 2007). To overcome this, the development of liposomal and nanoparticle formulations of curcumin has been investigated with reports of significant increases in its bioavailability (Bisht et al., 2007; Chen et al., 2009; Cui et al., 2009). Such strategies are also being employed to increase the oral bioavailability of resveratrol to improve its therapeutic potential (Santos et al., 2011). However, P-gp substrates (e.g., paclitaxel), delivered to P-gp overexpressing cells by nanoparticles, are susceptible to efflux by P-gp (Chavanpatil et al., 2006). It has also been shown that conjugation of negatively charged nanoparticles to glutathione led to nanoparticle efflux from the cell via MRP-transporters (Zhang et al., 2007; Holpuch et al., 2011). Some excipients are also potent ABC transporter inhibitors (Yamagata et al., 2007) and may be used in novel formulations to further improve PC bioavailability and targeted tissue distribution.

8. Conclusions

In conclusion, it is now apparent that the physicochemical properties of phytochemicals are not the only factors determining their oral bioavailability, and that there is a complex

interplay between these properties and the processes of metabolism and active transport in absorption, distribution and excretion, which determine the extent of exposure to their bioactive site(s) in the body. There is still much to be learned about the application of phytochemicals to the improvement of human health as these compounds have multiple complex effects on the body apart from their interactions with drug metabolizing enzymes and transporters. Despite limited data from human studies, the sheer amount and diversity of available phytochemicals continues to encourage researchers to look for new candidates with therapeutic potential and to improve their bioavailability and consequently their efficacy by developing new delivery systems.

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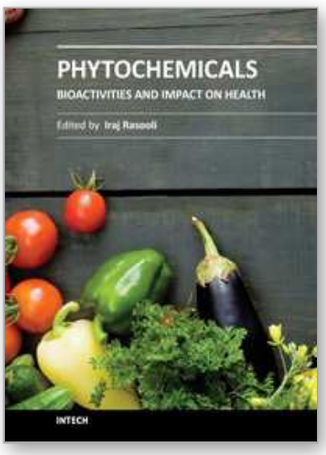

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Among the thousands of naturally occurring constituents so far identified in plants and exhibiting a long history of safe use, there are none that pose - or reasonably might be expected to pose - a significant risk to human health at current low levels of intake when used as flavoring substances. Due to their natural origin, environmental and genetic factors will influence the chemical composition of the plant essential oils. Factors such as species and subspecies, geographical location, harvest time, plant part used and method of isolation all affect chemical composition of the crude material separated from the plant. The screening of plant extracts and natural products for antioxidative and antimicrobial activity has revealed the potential of higher plants as a source of new agents, to serve the processing of natural products.

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