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Review Article

# The effect of food components on the absorption of P-gp substrates: a review

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## Abstract

P-glycoprotein (P-gp), a well characterized efflux mechanism which is functionally expressed in the intestinal epithelium, constitutes, along with intestinal metabolism, an important part of the biochemical barrier function of the intestinal mucosa. This efflux carrier may be responsible for limiting the bioavailability of several drugs after oral intake. Recently, increasing attention is being paid to the interaction of dietary components with the intestinal absorption of drugs. This review focuses on the modulating capacity of food components on the intestinal absorption of P-gp substrates. The possible P-gp inhibitory effects of several dietary constituents are discussed. In addition, this review will also focus on the effect of several bioflavonoids on the P-gp-mediated efflux of drugs. As the role of P-gp (and other efflux carriers, including multidrug resistance-associated proteins and breast cancer resistance protein) in limiting the bioavailability of drugs becomes more clear, more research is required firstly to identify the effect of dietary compounds on these efflux carriers and secondly to reveal the clinical relevance of this interaction.

## Introduction

More than 100 ATP-binding cassette (ABC) transporters have been characterized in bacteria, fungi, plants and animal cells. These transporters hydrolyse ATP to drive the flux of their substrates against a concentration gradient. The substrate range for these proteins is diverse and includes drugs, nutrients, amino acids, sugars and peptides. These transporters share a common organization and considerable amino-acid homology around the nucleotide-binding domain (Higgins 1992).

P-glycoprotein (P-gp), a 170-kDa protein that belongs to the superfamily of the ABC transporters, is believed to be responsible for multidrug resistance issues in the treatment of cancer (Ambudkar et al 1999). Besides its presence in several multidrug resistant cancer cells, P-gp is also expressed in normal tissue, including the liver, kidney, pancreas and blood–brain barrier (Thiebaut et al 1987; Schinkel et al 1997, Fromm 2000; Schuetz et al 2000). P-gp is also functionally expressed in the enterocytes that border the epithelium of the intestinal tract (Yumoto et al 1999), where it plays a role, together with intestinal metabolism, in the biochemical barrier function of the intestine. P-gp has been shown to limit the bioavailability of several drugs belonging to different chemical classes (e.g. ciclosporin A, talinolol, digoxin, vinblastine) (Spahn-Langguth et al 1998; Fromm 2000).

## Food–drug interactions

Recently, more attention has been paid to the characterization of food–drug interactions. The various stages in which food can interact with a co-administered drug occur before and after gastrointestinal absorption, during distribution, during metabolism and during elimination.

At the level of absorption, food–drug interactions can be classified into 5 categories: those causing reduced, delayed, increased and accelerated drug absorption, and those in which food has no effect (Welling 1996). Decreased drug absorption can be due to drug instability in gastric fluids, complexation interactions (e.g. between drugs and

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metal ions or dairy products), reversible or irreversible binding to dietary compounds (pectins, fibres) and increased viscosity of the lumenal content (Reppas et al 1998; Singh 1999). Delayed drug absorption usually results from a slower gastric emptying rate or increased gastric pH resulting from the ingestion of food (e.g. weakly basic drugs have slower dissolution rates at higher pH). The intestinal uptake of poorly soluble drugs can be increased by intake of food as a result of the secretion of bile salts (Fleisher et al 1999).

Although there is a vast amount of literature (for reviews see Fleisher et al 1999; Singh 1999; Evans 2000), there is still no rational scientific basis to predict the effect of food on a particular chemical entity or a chemical class of therapeutic agents. In this review, we will focus on the effects of food on drug absorption, more specifically at the level of intestinal P-gp.

## Interaction of food components with P-gp-mediated efflux

Over the last few years, the effect of natural products in cancer treatment or prevention has been extensively studied. Several compounds were also studied for their effect on P-gp-mediated efflux. The mechanisms by which food can interact with P-gp are yet unknown. Several mechanisms for interaction with P-gp have been described for other inhibitors, but not for food components. Possible mechanisms of action include downregulation of intestinal P-gp expression, competitive inhibition with other P-gp substrates and alteration of the membrane fluidity.

As many compounds can influence intestinal metabolic activity, this effect is also noted for several food compounds having a modulatory effect on P-gp. Various substrates have been used to assess the effect of food components on P-gp, including digoxin, ciclosporin A, talinolol, rhodamine-123, doxorubicin and vinblastine. An overview of the effect of food compounds on P-gp is given in Table 1. The food–drug interactions will be discussed in more detail in the following paragraphs.

### *Rosemary extract*

A good example of food–drug interactions at the level of P-gp can be found in the inhibiting effect of a methanolic rosemary extract on the P-gp-mediated efflux of doxorubicin, paclitaxel and vinblastine (Plouzek et al 1999). In the presence of rosemary extract, an increased intracellular accumulation of these P-gp substrates, and a decreased efflux of doxorubicin, could be observed. In an attempt to identify the compound responsible for the P-gp-inhibiting effect of rosemary extract, anti-

**Table 1** Overview of the effect of food compounds on P-gp.

| Product | Effect on P-gp | Study model | References |
|---|---|---|---|
| Green tea | Inhibition | In-vitro (rhodamine-123, vinblastine) | Jodoin et al 2002 |
| Rosemary extract | Inhibition | In-vitro (doxorubicin, vinblastine) | Plouzek et al 1999 |
| St John's wort | Induction | In-vitro (rhodamine-123) | Perloff et al 2001 |
| | | In-vivo (digoxin) | Johne et al 1999; Durr et al 2000 |
| Grapefruit juice | No effect | In-vivo (digoxin) | Becquemont et al 2001 |
| | | In-vitro (saquinavir) | Eagling et al 1999 |
| | Stimulation | In-vitro (vinblastine, digoxin, ciclosporin A) | Soldner et al 1999 |
| | Inhibition | In-vivo (ciclosporin A, talinolol, dextromethorphan) | Edwards et al 1999; Spahn-Langguth & Langguth, 2001; Di Marco et al 2002 |
| | | In-vitro (vinblastine, rhodamine-123, saquinavir) | Ohnishi et al 2000; Takanaga et al 1998; Tian et al 2002 |
| Grapefruit extract (standardized) | No effect | In-vitro (ciclosporin A) | Deferme et al 2002a |
| Seville orange juice | No effect | In-vivo (ciclosporin A) | Malhotra et al 2001; Edwards et al 1999 |
| | Inhibition | In-vitro (vincristine, vinblastine) | Ikegawa et al 2000; Takanaga et al 2000 |
| | | In-vivo (dextromethorphan) | Di Marco et al 2002 |
| Orange juice | Inhibition | In-vitro (rhodamine-123, saquinavir) | Tian et al 2002 |
| | No effect | In-vivo (ciclosporin A) | Johnston et al 1986 |
| Orange extract (standardized) | Inhibition | In-vitro (ciclosporin A) | Deferme et al 2002a |
| Garlic extract (aqueous) | No effect | In-vitro (P-gp ATP-ase activity) | Foster et al 2001 |
| Chargrilled meat | No induction | In-vivo (mRNA levels in intestine) | Fontana et al 1999 |
| Strawberry extract (standardized) | Inhibition | In-vitro (ciclosporin A) | Deferme et al 2002a; Van Gelder et al 2002 |
| Dietary fatty acids | Inhibition | In-vitro (digoxin) | Vine et al 2002 |
| Milk | No effect | In-vivo (ciclosporin A) | Johnston et al 1986 |
| Anastasia green (sweet pepper) | Inhibition | In-vitro | Motohashi et al 2001 |
| Piperine (black pepper) | Inhibition | In-vitro (digoxin, ciclosporin A) | Bhardwaj et al 2002 |
| Peppermint oil | Inhibition? | In-vivo (increased absorption of ciclosporin A, not due to metabolism inhibition) | Wacher et al 2001 |
| Mint extract (standardized) | Inhibition | In-vitro (ciclosporin A) | Deferme et al 2002a |
| Apricot extract (standardized) | Inhibition | In-vitro, ex vivo, in situ (talinolol) | Deferme et al 2002b |

oxidant constituents of rosemary extract, including carnosol, carnosic acid and rosemarinic acid, were evaluated for their influence on P-gp activity. The efflux of doxorubicin was not inhibited by any of these compounds. More research is required to determine concentrations attainable in man, as well as to identify the compounds which are responsible for the P-gp-inhibiting effect of rosemary extract.

*St John's wort*

Recently, alarming news about another food–drug interaction could be heard: extracts of St John's wort (*Hypericum perforatum*), widely used in the treatment of depression as an over-the-counter drug, were able to induce P-gp transporter activity in the gastrointestinal tract after chronic treatment (Johne et al 1999; Perloff et al 2001; Turton-Weeks et al 2001; Ioannides 2002). In a single-blind, placebo-controlled parallel study, it was shown that the plasma AUC and $C_{max}$ of digoxin decreased by 25% after ten days of treatment with hypericum extract (Johne et al 1999). Co-administration of hypericum extract decreased indinavir AUC by 57% and estimated plasma trough values by 81% in healthy subjects (Piscitelli et al 2000). Acute heart and kidney transplant rejection due to decreased ciclosporin levels (reduction of more than 50%) with co-administration of St John's wort has been reported in several case studies (Breidenbach et al 2000; Ruschitzka et al 2000; Turton-Weeks et al 2001). In-vitro analysis of this adverse interaction revealed that P-gp and CYP3A4 could be induced at low, clinically relevant concentrations of St John's wort and hypericine, the presumed active moiety within St John's wort. P-gp expression was strongly increased in LS-180 intestinal carcinoma cells after 3 days of treatment (400% and 700% increase by St John's wort and hypericine, respectively) (Perloff et al 2001). Chronic treatment with St John's wort resulted in induction of CYP3A activity in the intestinal wall. However, CYP2C9, CYP1A2 and CYP2D6 activity remained unaltered (Wang et al 2001b).

*Garlic*

Garlic has been widely used as a flavouring agent, traditional medicine, and functional food to improve physical or mental well-being. Garlic and garlic products are generally accepted as safe. However, two HIV-positive patients taking ritonavir experienced serious dose-dependent adverse effects (nausea, vomiting and diarrhoea) after taking either fresh garlic or odourless soft liquid-filled garlic supplements (Laroche et al 1998). Subsequently, the effect of this garlic supplement on single-dose pharmacokinetics of ritonavir was evaluated in 10 healthy subjects (Foster et al 2001). Although no significant effect could be observed, there was a trend towards a lower AUC for ritonavir and a higher clearance in the presence of the garlic supplement. In a broad screening for the potential effect of 10 garlic products (aged, odourless, freeze-dried, oil) and 3 varieties of fresh garlic bulbs on cytochromes (CYPs), four garlic products (aqueous extracts of garlic capsules and the 3 fresh varieties) were also screened for their potential to interact with P-gp, based on an in-vitro colorimetric ATPase assay (orthovanadate-sensitive release of phosphate) (Foster et al 2001). Besides the observation that garlic components can affect CYP2C-, CYP2D- and CYP3A-mediated metabolism, only slight effects on P-gp could be observed. The long-term effects of fresh garlic and garlic products on enzyme induction or inhibition require further study.

*Chargrilled meat*

Since heterocyclic amines and polycyclic aromatic hydrocarbons, present in chargrilled meat, are substrates for inducible CYP1A and CYP3A enzymes, as well as for P-gp, Fontana and co-workers have investigated the effect of a chargrilled meat diet on the expression levels of these enzymes and P-gp in 10 healthy subjects (Fontana et al 1999). After 7 days of consumption of a diet enriched with chargrilled meat, no induction of CYP3A4, CYP3A5 or P-gp mRNAs or protein in the small intestine or colon, and no induction of hepatic CYP3A4 enzyme activity could be observed. However, all subjects showed an increased expression of CYP1A enzymes in the liver and small intestine.

*Dietary fatty acids*

Vine and colleagues evaluated the effects of diets containing saturated fatty acids, monounsaturated fatty acids and $\omega$-3 and $\omega$-6 polyunsaturated fatty acids on the intestinal permeability for marker drug compounds (mannitol, diazepam, glucose and digoxin) (Vine et al 2002). After a dietary period of 30 days, permeability for these marker compounds was evaluated in excised rat jejunum mounted in Ussing chambers. Addition of dietary fatty acids did not result in any change in the passive paracellular permeability of mannitol. In contrast, the efflux transport of digoxin, a P-gp substrate, was reduced by 20% in the lipid-fed rats, although there were no significant differences between the different lipid groups. In addition to these results, the transcellular diffusion of diazepam and the active absorption of D-glucose were significantly altered in rats fed diets supplemented with fatty acids (Vine et al 2002).

*Pepper*

Other dietary constituents have been evaluated for their possible effect on intestinal CYP3A4/P-gp. Piperine, a major component of black pepper (*Piper nigrum*) and long pepper (*Piper longum*), has been shown to decrease the polarity in transport of several P-gp substrates (digoxin and ciclosporin A) in the Caco-2 system, without compromising the integrity of the monolayers (Bhardwaj et al 2002). Piperine also inhibited the CYP3A4-mediated metabolism of verapamil in human liver microsomes. An in-vitro study with extracts of another pepper variant, namely Russian green sweet pepper (Anastasia Green), showed higher cytotoxic activity against two human oral tumour cell lines than against normal human gingival fibroblasts, suggesting their tumour-specific action (Motohashi et al 2001). The extract was divided into twenty fractions, of which three (H3, H4 and H5) reversed P-gp-mediated multidrug resistance more effectively than verapamil in mouse T-cell lymphoma.

*Peppermint*

Another interesting compound, which might have a P-gp modulating capacity, is peppermint oil. Peppermint oil is used as a carminative and gastric sedative, and it has broad application as a flavouring and taste-masking agent in foods and pharmaceutical preparations, and is a common oral antiseptic agent. Peppermint oil finds clinical use in the treatment of irritable bowel syndrome, dyspepsia and colon spasm, and it has been administered at doses up to 1200 mg daily without adverse effects (Wacher et al 2001). Peppermint oil has been shown to reduce ciclosporin hydroxylation in rat liver microsomes by 50% when used at concentrations of 1 $\mu g\,mL^{-1}$ (Wacher et al 2001). In a study of its influence on absorptive and secretory processes in rat small intestine, using Ussing chambers and brush-border membrane vesicles, the inhibitory effect of peppermint oil (0.5 and 1 $mg\,mL^{-1}$) on active glucose uptake was shown, as was an inhibition of secretion, which was consistent with a reduced availability of calcium (Beesley et al 1996). Concomitant administration of ciclosporin A and peppermint oil to rats resulted in a 2.5-fold increase and a 3-fold increase of the $C_{max}$ and AUC, respectively (Wacher et al 2001). Ketoconazole, a known CYP3A inhibitor, did not alter ciclosporin absorption, which may reflect poor metabolism of ciclosporin in rat intestinal tissue. It was concluded that inhibition of CYP3A was not the only mechanism by which peppermint oil enhanced ciclosporin oral bioavailability. However, it was suggested that P-gp inhibition was not the underlying mechanism responsible for this effect, but rather the muscle relaxing effect of peppermint oil.

*Grapefruit*

Grapefruit juice increases the oral absorption of several drugs (e.g. by inhibition of the CYP3A4-mediated metabolism) (Ameer & Weintraub 1997). However, contradictory results have been obtained in the evaluation of grapefruit juice as a P-gp inhibitor. In a comparison of the effect of grapefruit juice and Seville orange juice on the disposition of ciclosporin A in healthy subjects, Edwards and co-workers concluded that the increased AUC of ciclosporin after ingestion of grapefruit juice was due to P-gp inhibition (Edwards et al 1999). Co-administration of Seville orange juice did not result in a significant effect on ciclosporin disposition, although reduced CYP3A4 enterocyte concentrations (40%) were observed. The inhibiting effect of several grapefruit juice extracts on the P-gp-mediated efflux of vinblastine was shown in Caco-2 cells. The ethyl acetate extract of grapefruit juice exerted the largest effect on the apical-to-basolateral transport of vinblastine, followed by the diethyl ether and the methylene chloride extracts (Takanaga et al 1998). Using the specific P-gp substrate talinolol, Spahn-Langguth and Langguth were able to show that grapefruit juice enhances the intestinal absorption of this $\beta$-blocking agent in-vitro (Caco-2) as well as in-vivo (rats) (Spahn-Langguth & Langguth 2001; Wagner et al 2001). In the presence of grapefruit juice, a three-fold increase of the absorptive transport (apical to basolateral) of talinolol in the Caco-2 model, and a two-fold increase of the $C_{max}$ and AUC in-vivo in rats was observed. In contrast to the observations mentioned above, the results of an open randomized cross-over study comparing the effect of grapefruit juice consumption (versus water) on the pharmacokinetics of a single oral dose of digoxin in 12 healthy subjects showed that no significant effect of grapefruit juice could be observed on the $C_{max}$ and AUC of digoxin (Becquemont et al 2001). In another study, which included vinblastine, ciclosporin, digoxin, fexofenadine and losartan (CYP3A4/P-gp substrates), and felodipine and nifedipine (CYP3A4 substrates), it was shown that grapefruit juice is able to stimulate P-gp-mediated drug efflux, rather than to inhibit it (Soldner et al 1999). In the presence of grapefruit juice, the net efflux of all the CYP3A4/P-gp substrates was significantly increased, while no effect was observed on the flux of the CYP3A4 substrates.

*Orange*

As for grapefruit juice, contradictory results have been obtained in the evaluation of Seville orange juice as a P-gp inhibitor. In a study on the effect of the vehicle on the oral absorption of ciclosporin, Johnston and colleagues evaluated the influence of milk, milk with chocolate flavouring and orange juice (Johnston et al 1986). No difference in the pharmacokinetic parameters of absorption could be observed between the commercial preparation and the three solutions that were used. In another comparative study, the influence of ethyl acetate extracts of grapefruit juice and orange juice on the P-gp-mediated efflux of rhodamine-123, saquinavir and fexofenadine was evaluated (Tian et al 2002). The grapefruit juice and orange juice extracts inhibited the efflux of all three P-gp substrates from everted sacs of rat intestine. This effect was comparable with the effect of verapamil, a known P-gp inhibitor. In another study, which involved grapefruit juice and orange juice, the concomitant administration of these juices significantly increased the bioavailability of dextromethorphan (Di Marco et al 2002); it was concluded that both grapefruit juice and Seville orange juice are long-lasting, and perhaps irreversible, inhibitors of gut CYP3A4 or P-gp. In contrast to these results, Malhotra and co-workers could not observe any significant effect of common orange juice on the absorption of felodipine, whereas co-administration with Seville orange juice and grapefruit juice resulted in a significant increased absorption, probably due to the inactivation of intestinal CYP3A4 (Malhotra et al 2001).

*Standardized nature-identical fruit extracts*

Experiments with several food compounds often resulted in different outcomes (e.g. grapefruit juice, orange juice). This inconsistency may be due to variability in composition of the fruit, depending on several factors, including vintage, cultivar, preparation of the extract/juice and origin of the fruit (Ameer & Weintraub 1997). To circumvent this variability, a screening of several standardized fruit extracts with a well-defined and nature-identical composition has been reported (Deferme et al 2002a). Nature-identical extracts consist of a mixture of synthetic compounds whose quantitative and qualitative composition is com-

parable with the composition of natural fruit extracts. When screening the effect of 68 standardized fruit extracts in the in-vitro Caco-2 system, strawberry, mint, orange and apricot extract (1% in the apical compartment) were shown to have a significant effect on the P-gp-mediated secretory transport of ciclosporin A. Standardized grapefruit extract did not modulate the efflux of ciclosporin A across the Caco-2 monolayers. A standardized apricot extract was further evaluated for its P-gp-inhibitory effects in other absorption models (Caco-2 system, Ussing chamber model, and an in-situ intestinal perfusion system) using talinolol, a specific P-gp substrate that is not metabolized by CYP3A4, as a model compound for P-gp-mediated efflux (Deferme et al 2002b). Standardized apricot extract had a significant impact on the polarity in transport of talinolol in the Caco-2 system as well as in the Ussing chamber system at a concentration of 1%, without toxic effects for the monolayer/rat intestinal tissue. In the in-situ intestinal perfusion system (rat ileum), inclusion of 1% standardized apricot extract in the perfusion medium resulted in a three-fold increase of the absorption of talinolol. The P-gp inhibitory effect of this standardized apricot extract was comparable with the effect of verapamil in all three models.

### Effect of flavonoids on P-gp mediated transport

In the quest to identify the active ingredients of dietary compounds, several bioflavonoids have been evaluated for their potential P-gp-inhibiting effect (Table 2). Flavonoids are polyphenolic compounds, which are abundant in fruit (especially in *Citrus*), vegetables, nuts, flowers, wine and tea. They constitute an important fraction of man's normal food, with an average of 200 mg consumed in the

**Table 2** Overview of the effect of different flavonoids on P-gp-mediated efflux.

| Compound | Effect on P-gp | Substrates | References |
|---|---|---|---|
| **Flavones** | | | |
| Apigenin | No effect | Daunomycin | Tseng et al 2001 |
| Chrysin | No effect | Vincristine | Mitsunaga et al 2000 |
| | Inhibition | Daunomycin | Tseng et al 2001 |
| Heptamethoxy-flavone | Inhibition | Vinblastine | Takanaga et al 2000 |
| Luteolin | No effect | Daunomycin | Tseng et al 2001 |
| Morin | Inhibition | Daunomycin | Tseng et al 2001 |
| Nobiletin | Inhibition | Vinblastine | Takanaga et al 2000 |
| Rhoifolin | Stimulation<br>Induction | Daunomycin | Tseng et al 2001 |
| Tangeretin | Inhibition | Vinblastine | Takanaga et al 2000; |
| | Stimulation | Tamoxifen | Bracke et al 1999 |
| **Flavonols** | | | |
| Galangin | Stimulation<br>Induction | Adriamycin, daunomycin | Critchfield et al 1994;<br>Tseng et al 2001 |
| Kaempferol | No effect | Daunorubicin, daunomycin | Wang E. et al 2001;<br>Tseng et al 2001 |
| | Stimulation | Adriamycin | Critchfield et al 1994 |
| | Inhibition | Hoechst 33342 | Shapiro & Ling 1997 |
| | Biphasic effect (stimulation at low concn, inhibition at high concn) | Vincristine | Mitsunaga et al 2000 |
| Myricetin | No effect | Daunomycin | Tseng et al 2001 |
| Quercetin | Inhibition | Adriamycin, daunomycin, Rhodamine-123 | Scambia et al 1994; Tseng et al 2001; De Vincenzo et al 2000 |
| | Stimulation | Adriamycin | Critchfield et al 1994 |
| | No effect | Saquinavir | Eagling et al 1999 |
| | Biphasic effect (stimulation at low concn, inhibition at high concn) | Vincristine | Mitsunaga et al 2000 |
| Rutin | No effect | Vincristine, adriamycin, daunomycin | Mitsunaga et al 2002; Tseng et al 2001; Scambia et al 1994 |
| **Flavanols** | | | |
| Catechin | No effect | Rhodamine-123 | Jodoin et al 2002 |
| Catechin gallate | Inhibition | Rhodamine-123 | Jodoin et al 2002 |
| Epicatechin | No effect | Rhodamine-123 | Jodoin et al 2002 |
| Epicatechin gallate | Inhibition | Rhodamine-123 | Jodoin et al 2002 |
| Epigallocatechin | No effect | Rhodamine-123, daunomycin | Jodoin et al 2002; Tseng et al 2001 |
| Epigallocatechin gallate | Inhibition | Rhodamine-123 | Jodoin et al 2002 |
| Silymarin | Inhibition | Daunomycin | Tseng et al 2001 |

**Table 2** (*Cont.*)

| Compound | Effect on P-gp | Substrates | References |
|---|---|---|---|
| **Flavanones** | | | |
| Hesperetin | Inhibition | Vincristine | Mitsunaga et al 2000 |
| | No effect | Daunomycin | Tseng et al 2001 |
| Hesperidin | No effect | Vincristine | Mitsunaga et al 2000 |
| Naringenin | Inhibition | Vinblastine | Takanaga et al 1998 |
| | No effect | Vincristine, daunorubicin, daunomycin | Mitsunaga et al 2000; Wang E. et al 2001; Tseng et al 2001 |
| Naringin | No effect | Daunorubicin, daunomycin | Wang E. et al 2001; Tseng et al 2001 |
| | Inhibition | Vinblastine, saquinavir | Takanaga et al 1998; Eagling et al 1999 |
| **Chalcones** | | | |
| Chalcone | Inhibition | Daunomycin | Tseng et al 2001 |
| | No effect | Rhodamine-123 | De Vincenzo et al 2000 |
| Phloretin | Inhibition | Daunomycin | Tseng et al 2001 |
| Isoflavones | | | |
| Biochanin A | Inhibition | Daunomycin | Tseng et al 2001 |
| Genistein | Inhibition | Rhodamine 123, daunorubicin, daunomycin | Castro & Altenberg 1997; Tseng et al 2001 |
| **Furanocoumarine derivatives** | | | |
| Bergamottin | No effect | Ciclosporin A, saquinavir | Malhotra et al 2001; Eagling et al 1999 |
| | Inhibition | Vincristine, vinblastine | Ikegawa et al 2000; Wang E. et al 2001; Ohnishi et al 2000 |
| Bergapten | Inhibition | Vinblastine | Ohnishi et al 2000 |
| Bergaptol | Inhibition | Vinblastine | Ohnishi et al 2000 |
| 6′,7′-Dihydroxybergamottin | No effect | Ciclosporin A | Malhotra et al 2001; Edwards et al 1999 |
| | Inhibition | Vincristine, vinblastine, saquinavir | Ikegawa et al 2000; Ohnishi et al 2000; Eagling et al 1999 |

daily Western diet (Scalbert & Williamson 2000). The structures of several flavonoid classes are illustrated in Figure 1. Flavonoids are known to exhibit a number of beneficial properties for human health, including antioxidant and free-radical scavenging actions. Additionally, flavonoids have been shown to exert anti-inflammatory, antiviral and anticancer activity (excellently reviewed by Middleton et al 2000). The flavour and fermentation industries are interested in these compounds primarily due to their contribution to such properties as flavour (e.g. flavanone glycosides), stability (e.g. flavanols), fragrance (e.g. phenols), toxicity (e.g. the flavone rutin) and colour (e.g. anthocyanins).

Recently, the antimutagenic activity of several polymethoxyflavonoids of Seville orange juice (*Citrus aurantium*), including sinensetin and nobiletin, has been reported (Miyazawa et al 1999). Interestingly, a decoction of Seville orange was investigated for its effect on the absorption and disposition of ciclosporin A in swine (Hou et al 2000). In this study it was shown that the $C_{max}$ of ciclosporin was increased by 67% when co-administered with the decoction, which resulted in acute toxicity of ciclosporin in 1 of 5 swine. Orange juice and orange-juice components have been shown to exert CYP3A4 inhibition (Edwards et al 1999; Guo et al 2001; Malhotra et al 2001), which has been attributed to the effect of 6′,7′-dihydroxybergamottin, a furanocoumarin also present in grapefruit juice and which has been described not to inhibit P-gp (Malhotra et al 2001). It was concluded that Seville orange juice did not interact with P-gp, in contradiction to grapefruit juice. However, other groups reported that Seville orange juice and its components (including tangeretin and nobiletin) do not inhibit CYP3A4, but that they inhibit P-gp (Ikegawa et al 2000; Takanaga et al 2000). An ethyl acetate extract of Seville orange juice significantly increased the uptake of vinblastine in Caco-2 cells. Several methoxyflavones, including tangeretin, heptamethoxyflavone and nobiletin, were identified as potent P-gp inhibitors, without influencing the 6$\beta$-hydroxylation of testosterone (probe for CYP3A4 activity) (Takanaga et al 2000). These results were confirmed in a study with adriamycin-resistant K562/ADM cells, in which the uptake of vincristine was increased by tangeretin, nobiletin and heptamethoxyflavone (Ikegawa et al 2000). Although bergamottin and 6′,7′-dihydroxybergamottin (grapefruit juice components) also showed a significant effect on vincristine uptake, these compounds were found to be less potent than the polymethoxyflavones.

Green tea consumption reduced tumour formation in skin, lung, liver, pancreas and the gastrointestinal tract. Polyphenols from green tea could have chemopreventive, anti-atherogenic, anticarcinogenic and antioxidant

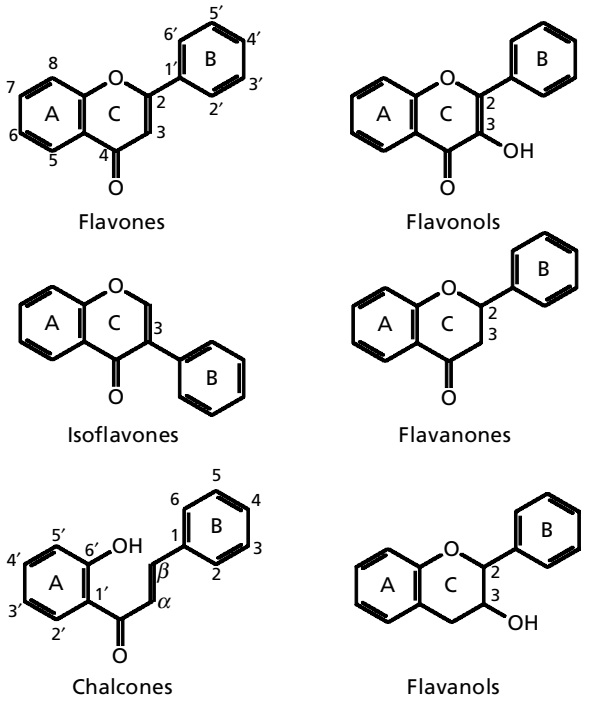


**Figure 1** Structures of the main flavonoid classes. Flavones are composed of three conjugated rings (A, B and C), the B-ring branched at position 2 of the C-ring. Flavonols contain an additional hydroxyl substituent at the position 3 of the C-ring. In isoflavones, the B-ring is branched at position 3 of the C-ring. The 2,3-bond of flavanones is reduced, thereby losing electron conjugation and ring planarity. As in flavanones, the 2,3-bond is reduced in flavanols, and they contain an additional hydroxyl substituent at position 3 of the C-ring, as in the flavonols. However, the carbonyl at position 4 is deleted. In chalcones, the C-ring is open and the numbering is different.

properties (Jodoin et al 2002). Recently, the effect of green tea extract and constituents of green tea (polyphenols) on P-gp activity was investigated in the multidrug resistant cell line $CH^RC5$ and in the Caco-2 model. In the presence of polyphenols, a three-fold increase in the accumulation of rhodamine-123 could be observed. Epigallocatechin gallate, catechin gallate and epicatechin gallate were presumed to be responsible for this P-gp-inhibiting effect. Addition of epigallocatechin gallate resulted in potentiated cytotoxicity of vinblastine in $CH^RC5$ cells, and in increased absorption and accumulation of vinblastine in Caco-2 cells (Jodoin et al 2002). This latter effect was comparable with the effect obtained with valspodar, a known P-gp inhibitor.

Another study included the comparison of natural rodent diet (containing flavonoids) and artificial rodent diet (no flavonoids) on etoposide absorption in rats (Lo & Huang 1999). In in-vitro tests (everted gut sacs), addition of the natural diet and quercetin increased the absorption of etoposide. However, when rats were fed with the natural rodent diet for one week, no significant effect on absorption of etoposide could be observed. This may be due to the metabolism of the ingredients with modulating activity to their inactive forms, reducing the effect of natural rodent diet. It was concluded that feeding rats with natural or artificial rodent diet had no obvious effect on etoposide absorption in-vivo.

In a study, with a sensitive and a multidrug resistant human breast cancer cell line (MCF-7), the effect of a series of bioflavonoids on the P-gp-mediated transport of daunomycin was evaluated (Tseng et al 2001). In this investigation, it was shown that biochanin A, genistein, morin, quercetin, phloretin, chalcone, chrysin and silymarin significantly increased the intracellular accumulation of daunomycin in the multidrug resistant cells. Following a 24-h incubation period, chalcone and phloretin decreased the expression of P-gp. In contrast to these observations, galangin and rhoifolin were shown to decrease the intracellular accumulation and to increase the P-gp expression after 24 h. The other flavonoids tested (hesperetin, myricetin, rutin, apigenin, luteolin, kaempferol and epigallocatechin) affected neither the daunomycin accumulation in the cells, nor the P-gp expression (Tseng et al 2001).

In a very interesting study, Di Pietro and co-workers investigated the binding capacity of approximately 70 bioflavanoids to the nuclear binding domains of mouse P-gp, as well as the effect of the flavonoid substituents on this binding affinity and the effect of several flavonoids on the intracellular accumulation of daunomycin (Di Pietro et al 2002). The following sequence in affinity was obtained: chalcone > flavonol > flavone > isoflavone > flavanone. In addition, within the same class of flavonoids, the following order of efficiency of substituents was observed: alkoxyl, geranyl > dimethylallyl > halogen >

monolignol > methoxy > hydroxyl > glycosyl, showing that the hydrophobicity of the substituents was an important factor. For the binding affinities, as well as for the intracellular accumulation of P-gp substrates, a positive effect of prenylation was observed in all classes of bioflavonoids. In contrast to these observations, all forms of glycosylation at different positions dramatically altered the binding affinity (Di Pietro et al 2002).

The contradictory results obtained with several individual compounds, including the bioflavanoids, indicate the difficulty in identifying a single compound as the active ingredient of fruit extracts and standardized extracts. Most likely, a combination of several components is responsible for the P-gp-inhibitory effect of these extracts, as different components may exert a synergistic effect on P-gp-mediated efflux.

## Conclusion

In conclusion, it might be stated that contradictory results have been reported with several fruits and dietary flavonoids with respect to their modulatory effect on intestinal P-gp activity. For the flavonoids, a possible explanation for this difference in results may lie in the concentration-dependent effect of these flavonoids. Mitsunaga and co-workers found, in their study on the effect of bioflavonoids on vincristine transport across the blood–brain barrier, that a biphasic effect may occur: at high concentrations, several bioflavonoids, including kaempferol and quercetin, showed P-gp-inhibiting properties, while the use of these flavonoids at low concentrations resulted in P-gp stimulation (Mitsunaga et al 2000). Other explanations for the different outcomes can be found in the different models (e.g. different cell-culturing models, in-vivo models, gastrointestinal models, blood–brain barrier models) and substrates that have been used for all these studies. Concerning the inconsistency of the results obtained with fruit juices and extracts (e.g. grapefruit juice, orange juice), the variability in the composition of the fruit might be a possible explanation, which can be solved by using standardized, nature-identical extracts (Deferme et al 2002a, b).

All these results obtained with fruit juices, extracts and their components, including bioflavonoids, indicate that more research is required to identify the interaction of food compounds with the intestinal absorption (and metabolism) of P-gp substrates. Additional investigation is required to positively use these food–drug interactions as a strategy to enhance the bioavailability of P-gp substrates. Co-administration with food components which have an inhibitory effect on intestinal P-gp might indeed be a simple and safe strategy to increase the oral absorption of P-gp substrates.

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