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Inhibitory effect of fruit extracts on P-glycoprotein-related efflux carriers: an in-vitro screening

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Abstract

In this study, standardized food extracts were screened for their possible inhibitory effect on the P-glycoprotein (P-gp)-mediated efflux of ^{3}H-ciclosporin A (CsA) using the in-vitro Caco-2 model. CsA is commonly used as a substrate for P-gp-related efflux carriers and is characterized by a polarity in transport, the absorptive transport being much lower than the secretory transport (polarity factor: PF $\sim$ 7). Of the 68 tested, nine extracts showed a decreased efflux of CsA ($<$ 75 % of the reference value) and were retained for further experiments on the bidirectional transport of CsA across Caco-2 monolayers. Results of these experiments showed that strawberry, orange, apricot and mint extract exert an inhibitory effect on intestinal P-gp-related functionality (PF $<$ 4.2). The effect of apricot extract was also studied on the bidirectional transport of talinolol, a specific P-gp substrate; inclusion of 1 %, v/v, in the apical compartment of Caco-2 monolayers resulted in a significantly reduced polarity in the transport of talinolol (PF reference = 15.5; PF in the presence of apricot extract = 2.5). This study suggests that co-administration of fruit extracts might be a conceptually safe and useful strategy to enhance the intestinal absorption of P-gp substrates. More research is necessary to characterize the impact of this inhibition on P-gp-related efflux mechanisms in other absorption models (in-vitro and in-vivo) and to identify the compounds that are responsible for this inhibitory effect.

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Introduction

P-glycoprotein (P-gp) is a 170 kDa transport protein belonging to the superfamily of the ABC-transporters. This efflux mechanism is believed to play a major role in the occurrence of multidrug resistance in the treatment of cancer (Silverman 1999; Szabo et al 2000). Moreover, P-gp is functionally expressed in the small intestine (Suzuki & Sugiyama 2000), renal epithelium (Aszalos & Ross 1998), the blood–brain barrier (Fromm 2000) and several other tissues in the human body (Krishna & Mayer 2000). In addition to many antitumour drugs (e.g. etoposide, doxorubicin, paclitaxel), drugs of totally different classes are transported by P-gp, including talinolol (β-blocking agent), ciclosporin A (CsA; immunosuppressive agent), and digoxin (cardiovascular drug) (Arimori & Nakano 1998).

Verapamil, a calcium-channel blocking agent, was the first compound described to have a P-gp-modulating effect (Tsuruo et al 1981). Several other compounds have since been identified to inhibit the efflux function of P-gp, including valspodar and LY335979 (Krishna & Mayer 2000). Over the next few years, several newly developed drugs will probably become available to overcome P-gp-related multidrug resistance in the treatment of cancer (Green et al 2001).

The importance of food effects and food–drug interactions at the level of the intestinal mucosa has recently been identified (Shimizu 1999; Singh 1999; Wagner et al 2001). Food can affect the absorption of drugs in several ways. The co-administration of drugs with food can lead to decreased (e.g. furosemide, erythromycin), increased (e.g. carbamazepine, saquinavir), delayed (e.g. ketoconazole, nifedipine) or accelerated (e.g. levodopa, theophylline) absorption of the drug, owing to several mechanisms, including pH effects in the stomach, intestinal motility changes, splanchnic and intestinal blood

flow changes (Singh 1999). In most cases, the effects of food on the bioavailability of a drug depend to a great extent on the physicochemical properties of the drug.

The intake of food can also influence the metabolism of drugs. A classic example of this food–drug interaction is the inhibition of cytochrome P450 (CYP) enzymes by grapefruit juice (Ameer & Weintraub 1997). Food components can have beneficial effects on several types of tumour, on prevention as well as on treatment. Recently, the suppressive effect of mandarin juice on chemically induced pulmonary tumourigenesis has been described (Kohno et al 2001). Compounds found in cocoa and chocolate are reported to inhibit the growth of human colonic cancer cells (Carnésecchi et al 2002). The possible protective compounds in vegetables and fruits include a variety of phytochemicals (Potter 1997). Carotenoids, which are abundant as pigments in plants, have been described to be responsible for lower incidence of lung cancer with higher consumption of vegetables and/or fruit (Voorrips et al 2000). A number of flavonoids are potential antioxidants and could scavenge free radicals and chelate metal ions (Husain et al 1987). Recently, polyphenols present in vegetables and fruits have attracted increased attention because of their potent antioxidant and antimutagenic properties (Rice-Evans et al 1995; Stoner & Mukhtar 1995). For example, grape seed extracts possess antitumour promoting activity owing to their strong antioxidant effect (Zhao et al 1999). Garlic extract, used since ancient times as a spice and for its medicinal properties, has been demonstrated to have chemopreventive potential against chromosomal mutations (Shukla & Taneja 2002). Many more examples of the chemopreventive properties of food, especially fruit and vegetables, can be found in the literature.

Several interactions between food and P-gp have also been described. For example, the use of St John's wort, an effective antidepressant, is known to induce the expression of P-gp, which can result in lower bioavailability of co-administered drugs, including indinavir, CsA and digoxin (Perloff et al 2001). The inhibition and reversal of P-gp by rosemary extract has been reported (Plouzek et al 1999). Orange juice, grapefruit juice and extracts, and several compounds of these citrus fruits have been investigated for their inhibitory effect on P-gp-related efflux mechanisms (Ikegawa et al 2000; Mitsunaga et al 2000; Takanaga et al 2000; Spahn-Langguth & Langguth 2001). The results obtained with these citrus fruits in studies performed by different researchers were not, however, completely corresponding. The inconsistency may be owing 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).

In this study, standardized fruit extracts (synthetic mixtures with a constant composition of compounds present in natural fruit) were evaluated for their inhibitory effect on P-gp-related efflux carriers. Screening with these extracts can be considered as screening with libraries. The use of these fruit extracts offers the following advantages: (i) the composition is known and reproducible; (ii) a combination of effects by compounds can be tested simultaneously; and (iii) relatively low toxicity is expected. To assess the influence of these fruit extracts on P-gp-related efflux mechanisms, a cell culture model (Caco-2 model) was used. This in-vitro system, which is a generally recognized model used to study the intestinal absorption of drugs, overexpresses P-gp at the apical side of the monolayer, causing a polarity in transport of P-gp substrates, the absorptive transport being much lower than the secretory transport.

Materials and Methods

Materials

All chemicals used for culturing the Caco-2 cells were purchased from InVitrogen (Merelbeke, Belgium). Cell culture medium consisted of Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 1% MEM non-essential amino acid solution and 100 IU mL^{-1} penicillin–streptomycin. Transport medium consisted of Hanks' balanced salt solution containing 25 mM D-(+)-glucose (Sigma Chemical, St. Louis, MO, USA) and 10 mM Hepes; pH was adjusted to 7.4 at 37°C with sodium hydroxide (0.5 M) (BDH, Poole, UK).

Talinolol was a kind gift from Arzneimittelwerk Dresden (Radebeul, Germany). Fruit extracts were obtained from Perlarom (Louvain-la-Neuve, Belgium), Givaudan (Dubendorf, Switzerland), International Flavors (Hilversum, The Netherlands), Universal Flavors (Heverlee, Belgium), Robertet (France) and Quest International (Naarden, The Netherlands). Their quantitative and qualitative composition is well defined and is nature-identical. This means that they consist of a mixture of synthetic compounds whose quantitative and qualitative composition is comparable with the composition of natural fruit extracts. The extracts were applied as a 1% aqueous solution (1%, v/v, in case of liquid extracts; 1%, w/v, in case of solid extracts). [^{3}H]-CsA (7 Ci $mmol^{-1}$) was purchased from Amersham Life Science (Gent, Belgium). Unlabelled CsA was obtained from Glaxo Wellcome (North Carolina, USA). Valspodar (also known as PSC833) was provided by Novartis Pharmaceuticals Corp. (Basel, Switzerland).

Caco-2 cell culture

Caco-2 cells were purchased from Bio-Whitakker (Walkersville, MD, USA). Cell culturing conditions were performed as previously described (Deferme et al 2002). Briefly, Caco-2 cells were grown in 75-cm^2 culture flasks at 37°C in an atmosphere of 5% CO_2 and 90% relative humidity. Cells were passaged every 3–4 days (at 70–80% confluence) at a split ratio of 1:7. Cells were negative for *Mycoplasma* infection.

Transport experiments

For transport experiments, Caco-2 cells were plated at a density of 40 000 cells cm^{-2} on Costar Transwell membrane inserts (0.2 μm pore diameter, 12 mm diameter; Corning Inc., NY, USA). Confluence was reached within 3–4 days

Table 1 Secretory transport of ciclosporin A (1 μM) across Caco-2 monolayers in the absence (reference) and presence of fruit extracts (1% in the apical compartment).

Extract	Brand	Secretory transport (%)±s.d.
Reference	–	100.0±7.9
Acerola	Perlarom	112.2±5.2
Advocate	Perlarom	110.1±13.8
Anise	Perlarom	85.6±5.1
Apple	Perlarom	113.9±2.4
Apricot 1	**Givaudan**	**58.4±13.4**
Apricot 2	International Flavors	82.6±2.5
Apricot 3	Perlarom	99.5±15.2
Apricot 4	**Perlarom**	**73.6±9.4**
Asparagus	Givaudan	94.9±7.5
Baikal	Perlarom	96.6±5.1
Banana 1	Givaudan	109.9±18.5
Banana 2	Perlarom	112.4±5.8
Banana 3	Perlarom	110.6±16.8
Blackberry	Perlarom	102.5±3.8
Black Currant	Perlarom	124.5±2.4
Bouratino	Perlarom	111.6±18.1
Caramel	Perlarom	99.4±8.1
Carrot	Givaudan	78.0±11.9
Cherry 1	Perlarom	90.7±2.7
Cherry 2	Perlarom	85.1±7.3
Coconut	**Perlarom**	**67.8±6.9**
Coffee	Perlarom	75.2±5.7
Cola	**Perlarom**	**67.3±7.7**
Cranberry	Perlarom	112.8±18.9
Feijoa	Perlarom	116.2±11.5
Forest fruits	International Flavors	100.2±10.5
Garlic	Givaudan	111.8±6.1
Grape 1	Givaudan	80.2±11.4
Grape 2	International Flavors	84.2±4.9
Grapefruit 1	Robertet	99.7±8.2
Grapefruit 2	Robertet	104.5±10.2
Grapefruit 3	Perlarom	105.7±5.5
Green Tea	Perlarom	107.4±3.5
Grenadine 1	International Flavors	125.5±11.1
Grenadine 2	Perlarom	84.9±6.8
Guarana	Perlarom	82.9±9.3
Hazelnut	Givaudan	88.1±8.7
Kiwi	**Perlarom**	**64.0±5.5**
Kombucha	Perlarom	130.9±31.8
Leek[a]	Givaudan	118.5±6.1
Lemon	Perlarom	128.8±7.6
Lime	Perlarom	75.6±7.6
Mango	Perlarom	93.5±9.0
Melon	Perlarom	139.0±13.7
Mint	**Perlarom**	**62.3±6.6**
Mulberry	Perlarom	111.7±4.8
Nutmeg	Perlarom	106.8±12.3
Olive Oil	Givaudan	143.1±6.0
Onion[a]	Givaudan	106.2±6.1
Orange 1	**Givaudan**	**47.8±12.4**
Orange 2	Perlarom	83.4±16.4
Orange 3	**Perlarom**	**64.1±9.4**
Passionfruit	Givaudan	118.1±11.5
Peach	Perlarom	112.2±7.5
Pear	Quest International	133.5±35.4
Pineapple 1	Perlarom	138.4±28.3
Pineapple 2	Perlarom	108.9±9.3
Pineapple 3	Perlarom	92.5±6.8
Plum	Universal Flavors	98.6±5.8
Red fruits[a]	Perlarom	95.5±5.1
Rhubarb	Givaudan	113.2±6.9
Strawberry 1	**Givaudan**	**59.5±6.7**
Strawberry 2	Perlarom	111.5±12.4
Strawberry 3	Perlarom	141.9±14.5
Tangerine	Perlarom	85.1±15.7
Tropical fruits	Perlarom	116.8±9.9
Vanilla	Perlarom	88.4±11.5

Results are expressed as a percentage of the reference±s.d. (n = 3). Extracts indicated in bold have a possible inhibitory effect on P-glycoprotein; [a]decreased TEER values (< 50% of the initial values).

after seeding and the monolayers were used for the experiments 21–25 days after seeding. Cell passages between 85 and 110 were used in the experiments. Transepithelial electrical resistance values (TEER values) were measured with an EndOhm Voltohmmeter (WPI, Aston, UK). Only monolayers with TEER values higher than 250 Ω cm^{-2} were used. All volumes amounted to 0.5 mL at the apical side of the monolayer and 1.5 mL at the basolateral side. In order to study the presence of active efflux mechanisms, CsA (1 μM) and talinolol (100 μM) were used as model compounds of the P-gp efflux carrier (Spahn-Langguth & Langguth 2001; Ingels et al 2002).

For the screening experiments with CsA, the monolayers were rinsed three times with transport medium, and cells were incubated for 30 min with transport medium before the TEER measurement. A 30-min pre-incubation step in the absence (reference) or presence of the food extract (1% in the apical compartment) was performed and TEER values were measured again. Transport was initiated by adding [^{3}H]-CsA (0.1 μCi) together with unlabelled CsA to the donor compartment to a final concentration of 1 μM. TEER values were measured at the end of the incubation step. Following incubation (60 min), the samples in the acceptor compartment were removed via multiple pipetting with 200-μL disposable pipette tips and placed (together with the tips) in scintillation vials (16 mL scintillation liquid, Ready Safe; Beckman, Fullerton, CA, USA) for liquid scintillation counting (Liquid Scintillation Counter, Wallac 1410, Beckman, Fullerton, CA, USA). All solutions of CsA were made in siliconized glass tubes to decrease adsorption of CsA. To ensure total recovery of [^{3}H]-labelled CsA in the basolateral acceptor compartment, 10 μL of a 1 mM unlabelled CsA solution in dimethylsulfoxide (DMSO) and 200 μL DMSO were added to the wells for 1 h before collecting the samples.

For the transport experiments with talinolol, the monolayers were rinsed three times with transport medium and cells were incubated for 30 min with transport medium before TEER measurement. A 30-min pre-incubation step in the absence (reference) or presence of apricot extract

(1% in the apical compartment) or valspodar (10 μM) was performed and TEER values were measured again. Transport was initiated by adding talinolol (100 μM) to the donor compartment and TEER values were measured at the end of the incubation step. Following incubation (120 min), samples in the acceptor compartment were taken and analysed by direct injection onto an HPLC system, as described below. As an additional control of the monolayer integrity, sodium fluorescein fluxes were measured at the end of the experiment. Sodium fluorescein (1 mg mL^{-1}; UCB, Belgium) was added to the apical compartment and, after 60 min, samples were taken from the basolateral compartment, followed by TEER measurements. The amount of sodium fluorescein appearing in the basolateral compartment was measured by UV spectrophotometry (Uvikon 810P spectrophotometer; Kontron Instruments, Watford, UK) at 490 nm. Sodium fluorescein flux values across the monolayers were typically below 0.6% h^{-1} cm^{-2}.

HPLC analysis of talinolol

Concentrations of talinolol were determined using an HPLC system (Waters Associated Inc., Milford, MA, USA) with fluorescence detection (λ_{ex} = 252 nm, λ_{em} = 332 nm) and the obtained peaks were integrated using a PC running Waters Millennium chromatography software (Waters Associated Inc). The column used was an Alltech Platinum C8 column (150 mm × 4.6 mm, 4 μm) (Alltech Associates, Lokeren, Belgium). The flow rate was 1 mL min^{-1}, and the mobile phase consisted of 75% KH_2PO_4 (10 mM, pH 3.5) and 25% acetonitrile. All water was purified by a Maxima system (Elga Ltd, High Wycombe, Bucks, UK). The volume injected was 100 μL. The retention time of talinolol under these conditions was 11 min. Intra-day repeatability of the HPLC method, expressed as relative standard deviation, amounted to 0.17% and 0.70% for 1250 nM and 150 nM, respectively, while the inter-day repeatability amounted to 2.2% and 4.1% for 1250 nM and 150 nM, respectively.

Calculations

Results of the screening experiments with CsA are expressed as a percentage of the reference value (= 100%). Results of the bidirectional transport experiments with CsA and talinolol are expressed as permeability coefficients (in cm s^{-1}), which were calculated as follows:

$$P_{app} = (\Delta Q/\Delta t) \times (1/(A \times C_0))$$

where ΔQ is the amount of drug appearing in the acceptor compartment (nmol), Δt is the incubation period (s), C_0 is the initial concentration in the donor compartment (μM) and A the surface area (cm^2) across which the transport occurred. All values are expressed as mean ± s.d. (n = 3). Polarity factors (PF) were calculated as the ratio of the P_{app} value for the secretory transport and the P_{app} value for the absorptive transport.

Statistical analysis

After performing analysis of variance tests ($P < 0.05$), a multiple comparisons test (Dunnett's test) was performed to compare the effects of the different conditions with the reference. Differences were considered significant at a level of 95% ($P < 0.05$). To mutually compare the effect of apricot extracts 1 and 4 on the bidirectional transport of talinolol, a Bonferonni test was performed at a significance level of 95% ($P < 0.05$).

Results and Discussion

In the initial screening experiments, the potential inhibitory effect of food extracts on P-gp-mediated efflux was studied by including the extracts (1%) in the medium at the apical side of the Caco-2 monolayers and measuring the secretory transport (from the basolateral to the apical compartment) of CsA, a commonly accepted substrate for P-gp-related transporters. Table 1 shows the results of the screening of 68 food extracts (different extracts of various brands) compared with the reference value (100%). A decrease in secretory transport of CsA indicates a potential inhibitory effect on P-gp-related efflux carriers, whereas an increase in secretory transport of CsA suggests an activation of the efflux mediated by P-gp-related transporters or an effect on the integrity of the monolayer (decreased TEER values). At a concentration of 1%, several extracts (leek, onion and red fruits extract) compromised the integrity of the Caco-2 monolayers; after an incubation period of 60 min, the TEER values of the monolayers treated with these extracts decreased to less than 50% of the initial values, thus excluding them from further experiments. For all the other extracts, no decrease in TEER values could be observed (data not shown). To further evaluate the possible inhibitory effect of the extracts on P-gp-related efflux mechanisms, the inclusion criterion was set at a secretory transport of CsA of less than 75% of the control condition. Only nine of the 68 tested extracts complied with this criterion: apricot 1 and 4, coconut, cola, kiwi, mint, orange 1 and 3, and strawberry 1. Surprisingly, none of the three tested grapefruit extracts exerted an inhibitory effect on the secretory transport of CsA mediated by P-gp-related efflux carriers. These results are in contrast with the conclusions of Spahn-Langguth & Langguth (2001). However, this observation is in agreement with the results of Becquemont and co-workers, who reported that grapefruit juice did not affect the in-vivo absorption of digoxin, another well known P-gp substrate (Becquemont et al 2001).

In a second set of experiments, extracts that had been shown to exert a modulatory effect on CsA efflux were also assessed for their effect on the absorptive transport of CsA (1% of extract in the apical compartment). Owing to inter-batch variability of the Caco-2 cells, only the results of the extracts that exerted a consistent inhibitory effect on the bidirectional transport of CsA are presented in Table 2. The extracts that most effectively reduced the polarity in transport of CsA (i.e. increased absorptive transport and

Table 2 Bidirectional transport of ciclosporin A (1 μM) across Caco-2 monolayers in the absence (reference) and presence of fruit extracts (1% in the apical compartment).

Extract	Absorptive transport P_{app} ($\times 10^6$ cm s^{-1})±s.d. (n = 3)	Secretory transport P_{app} ($\times 10^6$ cm s^{-1})±s.d. (n = 3)	Polarity factor±s.d.
Reference	2.11±0.17	14.69±1.03	6.96±0.59
Apricot 1	3.28±0.28*	11.05±0.36*	3.37±0.31
Apricot 4	3.70±0.09*	11.60±0.64*	3.14±0.19
Mint	3.16±0.23*	10.16±0.90*	3.22±0.37
Orange 1	1.98±0.20	7.73±0.48*	3.90±0.46
Orange 3	3.28±0.34*	11.17±1.07*	3.41±0.48
Strawberry 1	3.27±0.84*	13.68±1.25	4.18±1.13

*$P < 0.05$, statistically significant difference compared with the reference.

decreased secretory transport) were apricot (1 and 4), strawberry, mint and orange (1 and 3) (PF < 4.2, compared with PF = 6.96 for the reference).

For orange 1, this reduction in polarity was owing to a significantly decreased secretory transport of CsA ($P < 0.05$). Addition of orange 3 resulted in a significantly increased absorption of CsA together with a significantly decreased secretory transport ($P < 0.05$). The inhibitory effect of orange juice and compounds present in orange juice (including nobiletin and tangeretin) on the efflux of the P-gp substrate [^{3}H]vincristine has already been described by Ikegawa et al (2000). In addition, Takanaga et al (2000) reported an inhibiting effect of polymethoxylated flavones in orange juice on P-gp-mediated efflux of [^{3}H]vinblastine. However, as for grapefruit juice, contradictory results were obtained with Seville orange juice. This fruit juice is reported to have an inhibitory effect on CYP3A4, but not on P-gp (Edwards et al 1999; Malhotra et al 2001).

The addition of strawberry extract resulted in a decreased polarity in transport of CsA (PF = 4.18±1.13), which is mainly due to an effect on the absorptive transport of CsA ($P < 0.05$). Van Gelder et al (2002) recently described the enhancing effect of strawberry extract on the intestinal absorption of tenofovir disoproxil fumarate, an ester prodrug used for treatment of HIV infection. This absorption enhancement was not only owing to inhibition of the esterase-mediated degradation of tenofovir disoproxil fumarate, but also to an inhibitory effect on the efflux of this antiviral compound, mediated by P-gp-related efflux carriers.

Concerning the effect of mint on the modulation of the functionality of P-gp-related efflux mechanisms, Wacher et al (2002) recently described an enhancement of the CsA oral bioavailability in rats after co-administration of the drug with peppermint oil. Since the administration of CsA together with ketoconazole (which besides being a P-gp inhibitor is especially known as a CYP3A4 inhibitor) did not result in an effect on the absorption of CsA, it was concluded that inhibition of CYP3A4 metabolism was not the only mechanism by which peppermint oil enhanced the oral bioavailability of CsA. In addition to these data, our results (a significantly increased absorptive transport of CsA, together with a significantly decreased secretory transport, $P < 0.05$) suggest that the absorption enhancing effect of peppermint oil might be owing to an inhibitory effect of peppermint oil on the functionality of intestinal P-gp-related efflux carriers.

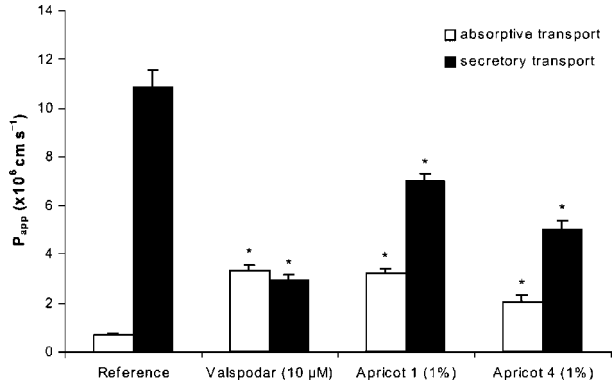

Figure 1 Bidirectional transport of talinolol (100 μM) across Caco-2 monolayers in the absence (reference) and presence of apricot extract (1%) and valspodar (10 μM) in the apical compartment. Results are expressed as P_{app} values ($\times 10^6$ cm s^{-1})±s.d. (n = 3). *$P < 0.05$, statistically significant difference compared with the reference.

A fourth extract with a possible P-gp-modulating effect was apricot extract, since inclusion of apricot extracts 1 and 4 resulted in a significant increase in absorptive transport of CsA together with a significantly decreased secretory transport ($P < 0.05$). Apricot extract was used in a third set of experiments to investigate its effect on the bidirectional transport of talinolol, a presumed selective substrate for P-gp that is not metabolized by CYP3A4 (Spahn-Langguth & Langguth 2001). The inhibitory effect of both apricot extracts (1%) on P-gp-related efflux carriers was studied in comparison with the reference value and a positive control (10 μM valspodar). Figure 1 shows a clear polarity in transport of talinolol, the absorptive transport being much lower than the secretory transport (PF = 15.5±1.2). The inhibitory effect of valspodar on P-gp-related mechanisms is indicated by an increase in ab-

sorptive transport, together with a decreased secretory transport, levelling the polarity in transport (PF = 0.9±0.1). The addition of apricot extract (1 and 4) in the apical compartment of the Caco-2 monolayers resulted in a significant increase in absorptive transport and a significant decrease in secretory transport of talinolol. The combination of these two effects resulted in a diminished polarity in transport of talinolol (PF of 2.2±0.2 and 2.5±0.4 for apricot 1 and 4, respectively). No statistically significant difference for the effect of apricot 1 and 4 on the bidirectional transport of talinolol could be observed ($P < 0.05$), showing that both apricot extracts exert an inhibitory effect on P-gp-related efflux mechanisms.

Conclusion

Although a lot of research has already been performed on the identification of food–drug interactions, many of these interactions and the mechanisms by which they occur remain to be explored. In this in-vitro screening study, we showed that several food extracts may have an inhibitory effect on P-gp-related efflux carriers including strawberry extract, orange extract, peppermint oil and apricot extract. More research has to be performed concerning the possible effect of these food extracts in other absorption models (in-vitro and in-vivo). The compounds (or combination of compounds) that are responsible for this inhibitory effect on P-gp-mediated efflux also remain to be identified.

This study indicates that the co-administration of food extracts with drugs known to be P-gp substrates might be a useful, safe and convenient way to enhance the intestinal absorption of these drugs.

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