The role of CYP3A4 and p-glycoprotein in food-drug and herb-drug interactions

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Abstract
Since grapefruit juice was first found to interfere with drugs in 1991, many other foodstuffs and herbs have been identified interacting with many drugs. Literature searches using Medline (1966-present) and Embase (1980-present) were conducted to obtain updated information on which components are responsible for these effects and the mechanisms involved. Foodstuffs, beverages and herbs can either inhibit the transport and metabolism of various drugs to increase their bioavailability or induce drug transport and changes in metabolism to reduce drug bioavailability. These effects are mediated mainly by cytochromes P450 (CYP) and the drug transporters p-glycoprotein (P-GP) and organic anion transporting polypeptide (OATP) in the intestine. Thus, grapefruit juice is known now to inhibit CYP3A4 and P-GP to increase drug bioavailability. However, it also inhibits OATP to increase drug bioavailability. While St John’s wort induces CYP3A4 and P-GP expression to decrease drug bioavailability, black pepper inhibits CYP3A4 and P-GP activities. The mechanisms could involve changes in either protein stability or gene expression. Limited studies have also been performed on several commonly used herbs. Goldenseal inhibits CYP3A4 by formation of metabolic-intermediate complex while ginkgo biloba activates CYP3A4 and P-GP. Seville orange also inhibits CYP3A4 and P-GP but the effect of garlic on CYP3A4 and P-GP has yielded conflicting results. Because a foodstuff or herb consists of many chemical and structural components, and each of its components could have different effect(s), the overall action of any single food or herb is the sum of those activities from each individual component that could induce or inhibit CYP3A4 and P-GP activities.

Foodstuffs and beverages may commonly be taken together with drugs. However, they may interact with many drugs, either reducing or increasing their bioavailability, an important pharmacokinetic parameter, and thus affect treatment efficacy or toxicity. The seriousness of food-drug interactions is dependent on the therapeutic index of each drug. With modern drugs generally having lower therapeutic indices, there is a greater possibility of toxic effects and changed treatment efficacy. These effects may lead to treatment failure or severe adverse effects, some of which may be life-threatening. Therefore it is important to evaluate the effects of individual foods on drug efficacies to avoid harmful effects and to elucidate the mechanism(s) involved so that food-drug effects can be predicted by patterns of actions and hence prevented.

The bioavailability of a drug is determined by its absorption, metabolism, distribution and excretion. These processes are mainly mediated by nuclear receptor-mediated detoxification system involving a variety of CYPs, conjugation enzymes and drug transporters. Among these, the cytochrome CYP3A4 and P-GP are most important. CYP3A4 accounts for about 60% of the breakdown of clinically used drugs. P-GP transports many drugs from the intestine into the blood. Therefore, it is very important for drug disposition and drug interactions in humans. This review focuses on discussing how several popular foodstuffs, beverages and herbs can affect both CYP3A4 and P-GP activities.

Although CYP3A4 and P-GP are distributed extensively in the human body, the main location for food-drug interaction is the intestine. Intestinal enterocytes located on the gastro-intestinal membrane represent the first cell lining that limits the entry of orally ingested compounds into the body. Both CYP3A4 and P-GP determine the bioavailability of many drugs that are substrates for them.
The role of CYP3A4 in drug metabolism

The CYP comprise a large group of heme-containing monoxygenase isoenzymes encoded by a gene superfamily. Generally, these enzymes biotransform lipophilic substrates of diverse structures into more hydrophilic metabolites in phase I reactions to facilitate subsequent excretion from the body and thus protect biological organisms from potentially toxic compounds. Such phase I reactions are also essential in the metabolism of endogenous sterols such as cholesterol, bile acids, fatty acids, prostaglandins, leukotrienes and retinoids as well as biogenic amines. These CYPs are important in drug-drug interactions as well as food-drug and herb-drug interactions since they catalyse metabolic effects on hundreds of thousands of substrates including most clinically used drugs in over 60 different types of reactions.

Because of the variety of CYP isoenzymes, a coding is used to describe the various forms, so that the acronym CYP3A4 stands for family 3, subfamily A and isoform 4. As the most abundant CYP both in the liver and the intestinal tract, CYP3A4 is responsible for the oxidative metabolism of a wide variety of substrates including steroids, foreign compounds and the majority of drugs. It is also intimately involved in chemical carcinogenesis in both the liver and extrahepatic tissues by its catalytic activities on many precarcinogens. CYP2C8 stands for family 2, subfamily C and isoform 8, and it has much narrower substrates in contrast to CYP3A4. These broad substrates of CYP3A4 are best explained in terms of the structure of CYP3A4 active site which has a much larger cavity able to bind a broad range of substrates compared with CYP2C8.

CYP3A4 catalyses many different types of chemical reactions including N-oxidation, C-oxidation, N-dealkylation, O-dealkylation, nitro-reduction, dehydration and C-hydroxylation. Following such reactions, drugs are generally more water soluble or possess lower biological activity. For example, carbamazepine is oxidised by CYP3A4 into carbamazepine-10, 11-epoxide (Figure 1). Inhibition of CYP3A4 by pomegranate juice has been shown to increase the blood concentration of carbamazepine in rats by inhibition of its oxidation.

Expression of CYP3A4 can be regulated via a number of different mechanisms ranging from transcriptional regulation to enzyme stability and inhibition. Expression is affected by many factors including nuclear receptors and hormones. Several nuclear receptors, which play important roles in drug-drug interactions and toxin excretion, are involved in CYP3A4 transcriptional regulation, and include pregnane X receptor (PXR), constitutive androstane receptor (CAR) and farnesol X receptor (FXR). In cultured hepatocytes, triiodothyronine was found to decrease CYP3A4 enzyme activity, protein mass and mRNA levels while dexamethasone and growth hormone increased CYP3A4 gene expression. CYP3A4 is also regulated by a large number of xenobiotics including many drugs.

Other common CYPs involved in drug metabolism include CYP2C8, CYP2C9, CYP2D, 1A and 2E1. CYP2C9 metabolises about 20% of clinically used drugs including diclofenac, ibuprofen, naproxen, phenytoin, piroxicam, S-warfarin and tolbutamide and CYP2C8 hydroxylates repaglinide, rosiglitazone and cerivastatin. The substrates for CYP2D6 include ciproprrol, codeine, debrisoquine, dextromethorphan, encaïnide, flecainide, fluoxetine, norfluoxetine, haloperidol, imipramine, nortriptyline, paroxetine, risperidone and thioridazine, while CYP1A2 catalyses caffeine, phenacetin, tacrine, theophylline metabolism and CYP2E1 acts upon dapsone. Induction or inhibition of these CYPs will thus affect the bioavailability of the corresponding metabolised drugs.

![Figure 1: Reaction catalysed by CYP3A4](image)
The role of P-GP in drug transportation

The absorption of drugs from the intestine is an important factor in determining their bioavailability. There are two types of transporters: efflux and influx.28 Efflux transporters include P-GP. These pump out drugs from the enterocytes into the lumen (Figure 2), thus decreasing their oral bioavailability. Influx transporters such as OATP enable enterocytes to uptake drugs from the lumen increasing their oral bioavailability.29,30,31,32

P-GP is a plasma membrane-bound protein, a member of a larger family of transporters encoded by multidrug resistance genes, MDR1 or ABCB1.15,33,34 It is a 170 kDa phosphorylated and glycosylated protein, 1280 amino acids long, which consists of two homologous halves of 610 amino acids joined by a flexible 60 amino acid linker. It is mainly found in the kidney, liver, small and large intestine, brain, testes and adrenal gland, uterus as well as in tumour cells.35 A nucleotide binding site in the protein can bind and use ATP as an energy source to transport certain hydrophobic substances away from the listed organs to protect them from harmful substances. Thus, P-GP plays an important role in drug absorption and disposition, acting as a biological barrier by expelling toxins and xenobiotics from cells.5,35,36 This effect may result in a decreased oral bioavailability of drugs that are substrates of P-GP. Chemicals known to be transported by P-GP have very diverse structures, but generally share the properties of being hydrophobic amphipathic (having both polar and non-polar components) molecules that are negatively charged.3 Such drugs subject to P-GP efflux include the cancer drugs – doxorubicin, daunorubicin, vinblastine, vincristine, actinomycin D, paclitaxel, teniposide and etoposide; the immunosuppressive drugs – cyclosporine A and tacrolimus, and steroids such as aldosterone, hydrocortisone, cortisone, corticosterone and dexamethasone. P-GP also transports the HIV protease inhibitors – amprenavir, indinavir, nelfinavir, ritonavir and saquinavir and the antibiotics – erythromycin, rifampicin. Cardiac drugs pumped include digoxin and quinidine along with the lipid lowering agents – lovastatin, simvastatin and atorvastatin. Others are the anthistimaine – terfenadine; the dopamine antagonist – domperidone; the antiemetetic – ondansetron; the anti-diarrheal agent – loperamide; the anti-gout agent – colchicine; the anti-helminthic agent - ivermectin; and the fluorescent dye - rhodamine-123.3

An understanding of the physiological regulation of these transporters is the key to elucidate the mechanisms of drug-, food-, and herb-drug interactions mediated by P-GP. P-GP-dependent drug transport activity depends on the level of the expression of the gene as well as the functionality of the expressed protein. Its activity is upregulated by many endogenous and environmental factors that evoke stress responses including cytotoxic agents, heat shock, irradiation, genotoxic stress, inflammation, inflammatory mediators, cytokines, growth factors and drugs.37 Well known inhibitors of P-GP include the immunosuppressant cyclosporin A, the calcium channel blocker verapamil, the anti-oestrogen tamoxifen, the antibiotic erythromycin, the antifungal ketoconazole, the antiarrhythmic agent quinidine and the progesterone antagonist mifepristone.3,38

OATPs are a family of proteins responsible for the transport of a large number of endogenous and xenobiotic compounds across cell membranes.39 So far, 9 OATPs have been identified in humans. OATP C and OATP 8 are mainly found in the liver while OATP B exists both in the liver and the intestine as identified from immunohistological data.39 The substrate range of OATP B is narrow, and includes pravastatin, fexofenadine, talinolol.40 The pH of the small intestine is a major factor regulating the activities of OATPs and is an important factor in how these interact with foods in the intestinal lumen.39,40

Grapefruit juice

A grapefruit juice-drug interaction was first reported in 1991 when used as a flavour supplement during a study of ethanol and felodipine interaction. A single glass of grapefruit juice caused a two-three fold increase in felodipine plasma levels compared to orange juice, which had no effect.41 Since then many drugs have been shown to have increased bioavailability affected by grapefruit juice.42,43 Its major effect was identified as the loss of CYP3A4 activity in the small bowel epithelium with a 47% decrease of parent drug in a healthy volunteer four hours after consuming grapefruit juice.44 The inhibition of CYP3A4 by grapefruit juice leads to an increased bioavailability of many drugs such as calcium channel antagonists, benzodiazepines, HMG-CoA reductase inhibitors, and cyclosporine.45 Interestingly, while atorvastatin bioavailability was increased by 83%, that of pitavastatin was not affected.46

A number of grapefruit juice chemical constituents have been studied to elucidate its effect. These include the flavonoids naringin, naringenin, quercetin and kaempferol, the furosoumarins bergamottin and 6,7-

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Figure 2: Drug pumped out from intestinal cells into lumen of gut
dihydroxybergamottin, and the bitter limonoids limonin and obacunone.54,56,57,58,59

Screening experiments led to the conclusion that the inhibitory effect was increased by hydroxyl substitution of the flavonoids. The inhibitory effects increased with increased number of hydroxyl groups as following flavone [1 OH] < apigenin [3 OH] < morin and quercetin [5 OH] < myricetin [6 OH].51 In addition, the flavanone glycoside naringin, with two phenolic hydroxyls, was weaker than its corresponding flavanone naringenin, which has three phenolic hydroxyls groups.50 Because naringenin is an aglycone of naringin, other explanations could exist such as polarity or effects of sugar residues. Both flavonoids tested acted in a dose-dependent fashion. None produced an effect equivalent to that of the grapefruit juice itself, suggesting that the action of the juice was caused by other more important components or was an additive effect of several different constituents.50

The furanocoumarins bergamottin and 6, 7-dihydroxybergamottin have also been studied for their inhibitory effect on CYP3A4 activities.53,54,55,56 While 6, 7-dihydroxybergamottin rapidly inhibited CYP3A4 activity within 30 minutes, bergamottin had a slower onset and exhibited substrate-dependent inhibition activity that peaked after three hours.51,54 Goosen et al. demonstrated that bergamottin contributed to the grapefruit juice-induced felodipine bioavailability.50

The effect on CYP3A4 was considered to be due mainly to grapefruit juice’s influence in the intestine for the reasons outlined below. Orally administered grapefruit juice increased the bioavailability of orally administered nicardipine but not by the intravenously administered drug in which case, it was only metabolised by liver CYP3A4.57 This could be explained by the fact that the content of CYP3A4 is lower in the liver than in the intestine.58 The area under the curve (AUC) of nicardipine was the pharmacokinetic parameter mainly changed, but its half-life did not alter. However, a recent study also showed that simvastatin metabolism by rat liver microsomes was inhibited by bergamottin, suggested that components of grapefruit juice may have a hepatic effect as well as an enteric effect.59

The active constituent 6,7-dihydroxybergamottin can bring about dose-dependent decreases in both CYP3A4 activity and protein mass in the human intestinal cell line, Caco-2, a cell culture that expresses catalytically active CYP3A4.42,50,60 This was demonstrated to be a post-transcriptional regulatory response. The mRNA levels of CYP3A4 did not change after grapefruit juice ingestion.61 In 10 healthy men, after drinking a glass of grapefruit juice three times a day for six days, the concentration of CYP3A4 from small bowel biopsy fell 62% from controls but no corresponding changes in CYP3A4 mRNA levels were detected.62

These studies of the effect of grapefruit juice on CYPs have also been extended to other CYPs. Thus, bergamottin inhibited CYP2B6 and CYP3A5 irreversibly by binding to both, as shown by liquid chromatography-mass spectroscopy analysis and SDS-polyacrylamide gel electrophoresis.63 In samples inactivated by bergamottin, both CYP2B6 and CYP3A5 apoproteins had increased by about 388 Da due to [14C] bergamottin irreversibly binding to the apoprotein. However, bergamottin had no effect on CYP2C19 activity and it increased the bioavailability of lansoprazole by an inhibition of its sulphoxidation, which is mediated by CYP3A4. Similarly it had no effects on its systemic pharmacokinetics, which is mainly under the control of CYP2C19.64,65

Grapefruit juice was also shown to inhibit the metabolism of drugs such as ritodrine.65 Sulphation of ritodrine in the intestinal mucosa is responsible for its low bioavailability (about 30%). In vitro studies have shown that recombinant human sulftotransferases 1A1 and 1A3 were inhibited by a 10% solution of grapefruit juice, as well as orange juice and green and black tea.66

Bergamottin, quercetin, kaempferol and naringenin from grapefruit juice have also been reported to modulate P-GP activity by directly interacting with the substrate binding site to block the transportation of several drugs.66,67 For example, all four compounds inhibited the intestinal transport of cyclosporine to increase its oral bioavailability, but had no influence on digoxin, probably because of its high inherent oral bioavailability.66

P-GP was recently shown to be regulated by changes in its mRNA levels.68 In the human immortalised tubular cell line HK-2, grapefruit juice decreased P-GP protein mass as well as mRNA levels in a dose-dependent fashion. Kaempferol and naringenin also decreased P-GP protein mass. These effects have been postulated to lead especially to increased cyclosporin A and vinblastine levels. However, recent work has shown that P-GP mRNA and protein levels in duodenal biopsy specimens did not change after six days of repeated grapefruit juice (900ml/day) administration.69 This controversy needs further study for clarification.

Recently, grapefruit juice was shown to reduce talinolol bioavailability rather than increase it.64 This may suggest that constituents in grapefruit juice preferentially inhibited an intestinal uptake process rather than affecting P-GP activity or concentration. Flavonoids reduced talinolol transport across CaCo-2 cells via organic cation transporter (OCT) –family.69 In a rat model, grapefruit juice also decreased the bioavailability of fexofenadine, which is a substrate for both the efflux transporter P-GP, and the influx transporter, OATP.70,71 Different volumes of grapefruit juice have been used to test its effect on the bioavailability of fexofenadine.72,73 The result showed that 300mL of grapefruit juice caused a decreased oral bioavailability of fexofenadine, probably
by inhibition of intestinal OATP-A. An increase in consumption volume produced additional inhibition.

In conclusion, patients taking drugs that are metabolised by CYP3A4 or transported by P-GP as well as OATP and especially those with a narrow therapeutic index should be advised to avoid drinking grapefruit juice.

St John’s wort

St John’s wort is a widely consumed antidepressant natural product derived from the flowering plant Hypericum perforatum. Various drug interactions caused by St John’s wort have been observed. For example, the herb markedly decreased the effective plasma concentrations of several drugs.

There are a dozen or so active chemicals in St John’s wort including flavonols, flavonol glycosides, biflavones, napthodanthrones, acylphloroglucinols and phenylpropanes. The active pharmacological components were identified as hyperforin and hypericin, through their inhibitory effect on the reassimilation of neurotransmitters in nerve synapses. Indeed, hyperforin is the chemical that activates the PXR with high affinity, i.e. a half-maximal effective concentration of 23 nM, makes it the most potent pregnane X receptor (PXR) activator found to date. Activated PXR in turn increases the gene expression of CYP3A4. However, in vitro experiment, acute exposure of hyperforin is a potent competitive inhibitor of CYP3A4, and quercetin a moderate inhibitor of CYP3A4. So the overall influence of St John’s wort could be the sum effect of its inhibitory and activating constituents.

In healthy subjects, long-term (14 days) administration of St John’s wort resulted in an induction of CYP3A4 as demonstrated by a markedly increased clearance of cortisone as detected by increased urinary 6-beta-hydroxycortisone/cortisone ratio and decreased oral bioavailability of midazolam. In animal experiments, three weeks treatment of St John’s wort to mice increased their CYP3A protein levels by six-fold.

Several studies have also shown that St John’s wort can induce P-GP synthesis in vitro and in vivo. In healthy volunteers, oral administration of St John’s wort extract at 900 mg/day for 14 days resulted in a 1.4-fold increase in intestinal P-GP expression. Treatment of LS-180 intestinal carcinoma cells with St John wort at 3-300 μg/ml or hypericin at 3-300μM also caused a four- to seven-fold increase in P-GP protein mass. The administration of St John’s wort extract to rats for 14 days resulted in a 3.8 fold increase in intestinal P-GP expression.

The effects of St John’s wort on P-GP and CYP3A4 were also shown in primary cultures of human hepatocytes to be mediated by activation of PXR. Two of its constituents, hyperforin and hypericin, inhibited efflux of the fluorescent markers daunorubicin and calcein-AM. In HepG2 cell line addition of St John’s wort or hyperforin increased mRNA levels of CYP3A4, 1A1, 1A2 and the multidrug resistance protein 2 (MRP2). Thus, it is possible that St John’s wort could activate PXR and subsequently upregulate a number of its target genes.

Black pepper

Black pepper, Piper nigrum, is a popular spice (world production was 47.6 million tonnes in 1991), but has been found to have broad effects on drug dispositions. Its major component, the piperidine amide piperine, was shown to increase the bioavailability of several drugs including theophylline, phenytoin, rifampicin and propanolol.

In humans, administration of piperine markedly increased the bioavailability of these four drugs. Following administration of piperine (20mg daily for seven days), a single oral dose of propranolol 40mg or theophylline (150mg) was given to normal subjects. With propranolol, an earlier tmax and a higher Cmax and AUC were observed, while with theophylline, a higher Cmax was observed, together with a longer elimination half-life and a higher AUC.

The mechanism of action was demonstrated to involve inhibition of CYP3A4 and P-GP. In human Caco-2 cells, piperine inhibited P-GP-mediated digoxin and cyclosporine transport. It also inhibited CYP3A4-mediated formation of verapamil metabolites D-617 and norverapamil in human liver microsomes, leading to increased plasma concentrations of verapamil.

Seville orange (Citrus aurantium)

Seville orange (Citrus aurantium) extracts have been used for herbal weight-loss products instead of ephedra (Ephedra sinica), which was recently banned by the FDA. The main effective components for such an effect are synephrine and octopamine. Although Seville orange is considered to be much safer, it has been also noted that Seville orange caused potential herb-drug interaction.

Seville orange has similar effects on CYP3A4 and P-GP as grapefruit juice. It contains 6’, 7’-dihydroxybergamottin as does grapefruit juice. In addition, it has bergaptene, which also inhibit CYP3A4. Thus, it may have even stronger inhibitory effect than that of grapefruit juice. So far, few studies have been performed. However, it has been shown to increase the bioavailability of felodipine and dextromethorphan. In the clinical trial, it has not affected cyclosporine as grapefruit juice did.

Goldenseal (Hydrastis canadensis)

Goldenseal (Hydrastis canadensis) rhizome extract is a common immunostimulant and anti-microbial herb. It is often used to treat symptoms of cold and influenza, such as cough and sore throats, as well as those of
Gastrointestinal infections such as stomach upset.\textsuperscript{73} It has also been combined with other herbs for the treatment of menstrual disorders, urinary infections, rheumatic and muscular pains. The active components are alkaloids hydrastine and berberine.\textsuperscript{93} However, it also affects other drugs through CYPs. Among 21 herbs tested against human hepatic microsomal CYP activities, goldenseal rhizome extract was the strongest to inhibit CYP3A4.\textsuperscript{92}

It has been demonstrated to inhibit CYP3A4 as well as other CYPs in an in vitro system.\textsuperscript{95,96,97} The CYP3A4 was strongly inhibited while CYPs2C9 and 2D6 were also moderately inhibited. The effect on CYP3A4 is mainly caused by hydrastine rather than berberine with IC50 30 μM compared to 400 μM. This is also supported by a small clinical trial in 12 volunteers that activities for CYP3A4 and 2D6 were strongly inhibited as indicated by 1-hydroxymidazolam/midazolam serum ratios and debrisoquin urinary recovery ratios.\textsuperscript{96}

The mechanism of the inhibitory effect of goldenseal is the rapid formation of CYP metabolic-intermediate (MI) complexes.\textsuperscript{96} Incubation of its major component hydrastine with human hepatic microsome showed MI complex formation, which has a peak absorbance at 455 nm. The effect is dose-dependent in the range of 33 to 333 μM and also time-dependent since the reaction reached a maximum at 4 minutes. Using heterogeneously expressed CYP3A4, CYP2C9 and CYP2D6 for the experiment, it was further shown that CYP3A4 is preferred for the formation of MI complex.

**Gingko biloba**

*Gingko biloba* leaf extract has antioxidant effects to improve micochondrial activity in blood and is used for the treatment of poor circulatory conditions.\textsuperscript{97,98} It also has neuroprotective effects and often used to treat dementias, decreased memory, cerebral insufficiency, anxiety/stress.\textsuperscript{99,100} The active components are ginkgo flavones (24%), which are free radical scavengers, and terpene lactones (6%), which inhibit platelet-activating factors and facilitate blood flow.

Ginkgo also modulates CYP3A4 and P-GP similar to St John’s wort. In rats, it has been shown to reduce the bioavailability of cyclosporine, a substrate of CYP3A4.\textsuperscript{101} In rats, co-administration of ginkgo (0.2g/kg) decreased AUC of cyclosporine by about 50%.\textsuperscript{101} While another study showed that co-administration of ginkgo with nifedipine, a CYP3A4 substrate but not P-GP, increased the bioavailability of nifedipine, indicating the inhibition of CYP3A4.\textsuperscript{102} *In vitro*, it has been shown that some components of ginkgo inhibited CYPs.\textsuperscript{103,104} In 18 healthy volunteers, ginkgo also induced CYP2C19 and decreased plasma concentration of omeprazole with increased 5-hydrxyomeprazole.\textsuperscript{105} However, it has no effect on CYP2C9 in clinical trials using flurbiprofen or tolbutamide as probes.\textsuperscript{106,107}

**Garlic (Allium sativum)**

Garlic is also a strong anti-oxidant agent mainly due to its component S-allyl cysteine. Thus, it can be use for the prevention and treatment of cancer.\textsuperscript{108} It has also been used for the prevention and treatment of cardiovascular diseases such as atherosclerosis.\textsuperscript{109}

Frost et al. showed the inhibitory role of garlic on several CYPs. It has affected the bioavailability of saquinavir but did not affect the pharmacokinetics of saquinavir.\textsuperscript{110,111} However, it is considered to be unlikely to inhibit CYPs in recent studies. In an *in vitro* study using human hepatic microsomes, of the eight garlic components tested, only S-methyl-L-cysteine and S-allyl-L-cysteine produced more than 50% inhibition at the concentration of 100 μM/L, which is much higher than *in vivo* exposure.\textsuperscript{112} In a clinical trial with 14 volunteers, administration of garlic extract (3x600mg twice-daily for 14 days) did not change the metabolism of CYP2D6 substrate dextromethorphan and CYP3A4 substrate alprozolam.\textsuperscript{113}

**Echinacea purpurea, Panax ginseng, Serenoa serrulate, Valeriana officinalis, Silybum marianum**

*Echinacea purpurea* has mild-moderate inhibition on CYP3A4.\textsuperscript{114,115} The kaempferol-like component of Panax ginseng has been shown to inhibit CYP3A4 and P-GP.\textsuperscript{116} Recently, *Panax ginseng* and *Panax quinquefolius* extracts were shown to have no effects on rat CYP2B1, CYP3A23 and CYP1A2.\textsuperscript{117} Clinical trials showed it is unlikely that ginseng produced CYP-mediated herb-drug interactions.\textsuperscript{118,119} Valerian, *Valeriana officinalis*, has demonstrable moderate effects on CYP3A4 or P-GP.\textsuperscript{93} Recently, Panax ginseng and *Panax quinquefolius* extracts were shown to have no effects on rat CYP2B1, CYP3A23 and CYP1A2.\textsuperscript{117} Clinical trials showed it is unlikely that ginseng produced CYP-mediated herb-drug interactions.\textsuperscript{118,119} Valerian, *Valeriana officinalis*, has demonstrable moderate effects on CYP3A4 or P-GP.\textsuperscript{93}

**Conclusion**

CYPs and drug transporters are important factors in drug metabolism and transportation. The interplay of these factors in the intestine determines the bioavailability of many drugs. Grapefruit juice inhibits both CYP3A4 and efflux transporter P-GP to decrease the bioavailability of their drug substrates. However, it also inhibits influx transporter OATP and thus decreases...
the bioavailability of drug substrates such as provastatin, fexofenadine and talinolol.

In contrast to grapefruit juice, St John’s wort induces both CYP3A4 and P-GP and the effect is to decrease the bioavailability of these same drugs. Its mechanism of action may involve activation of nuclear receptors. While 

Gingko biloba has similar effect as St John’s wort to activate CYP3A4 and P-GP, black pepper and Seville orange inhibit CYP3A4 and P-GP activities. Goldenseal also inhibits CYP3A4 by formation of metabolic-intermediate complex. But the effect of garlic on CYP3A4 and P-GP is not established.

As stated initially, foodstuffs and herbs may increase or decrease drug availability depending on the specific type of the interaction. Foodstuffs and herbs consist of many components, and each individual chemical constituent may have a different effect. The overall effects of a food or herb are thus the sum of each individual constituent that could induce or inhibit CYP3A4 and P-GP in the intestine. Therefore, they have to be evaluated individually.

Reference available at www.psa.org.au
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web wonders
by Karalyn Huxhagen

Chronic diseases

www.CCMDweb.org – this very useful web site encompassing many chronic diseases. It contains information on therapeutic guidelines, patient information and clinical updates. The site also contains interactive case studies and downloadable CME and is very user friendly.

www.blackdoginstitute.org.au/ – describes its work as ‘a clinical, research and educational body dedicated to improving understanding, diagnosis and treatment of depression and bipolar disorder (formerly called manic depression in severe cases)’. It is an excellent web site and is a great resource for patients, carers and health professionals working with mood disorders. Web sites discussed previously that complement this site are www.moodgym.anu.edu.au and www.beyondblue.org.au

The National Stroke Foundation can be found at www.strokefoundation.com.au . This site offers information for patients about stroke treatment, links to support groups and information and guidelines for health professionals.

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