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Herb-Drug Interactions

A Literature Review

Zeping Hu,[1] *Xiaoxia Yang*,[1] *Paul Chi Lui Ho*,[1] *Sui Yung Chan*,[1] *Paul Wan Sia Heng*,[1] *Eli Chan*,[1] *Wei Duan*,[2] *Hwee Ling Koh*[1] and *Shufeng Zhou*[1]

1 Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore
2 Department of Biochemistry, Faculty of Medicine, National University of Singapore, Singapore

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Abstract

Herbs are often administered in combination with therapeutic drugs, raising the potential of herb-drug interactions. An extensive review of the literature identified reported herb-drug interactions with clinical significance, many of which are from case reports and limited clinical observations.

Cases have been published reporting enhanced anticoagulation and bleeding when patients on long-term warfarin therapy also took *Salvia miltiorrhiza* (danshen). *Allium sativum* (garlic) decreased the area under the plasma concentration-time curve (AUC) and maximum plasma concentration of saquinavir, but not ritonavir and paracetamol (acetaminophen), in volunteers. *A. sativum* increased the clotting time and international normalised ratio of warfarin and caused hypoglycaemia when taken with chlorpropamide. *Ginkgo biloba* (ginkgo) caused bleeding when combined with warfarin or aspirin (acetylsalicylic acid), raised blood pressure when combined with a thiazide diuretic and even caused coma when combined with trazodone in patients. *Panax ginseng* (ginseng) reduced the blood concentrations of alcohol (ethanol) and warfarin, and induced mania when

used concomitantly with phenelzine, but ginseng increased the efficacy of influenza vaccination. *Scutellaria baicalensis* (huangqin) ameliorated irinotecan-induced gastrointestinal toxicity in cancer patients.

Piper methysticum (kava) increased the 'off' periods in patients with parkinsonism taking levodopa and induced a semicomatose state when given concomitantly with alprazolam. Kava enhanced the hypnotic effect of alcohol in mice, but this was not observed in humans. *Silybum marianum* (milk thistle) decreased the trough concentrations of indinavir in humans. Piperine from black (*Piper nigrum Linn*) and long (*P. longum Linn*) peppers increased the AUC of phenytoin, propranolol and theophylline in healthy volunteers and plasma concentrations of rifamipicin (rifampin) in patients with pulmonary tuberculosis. *Eleutheroccus senticosus* (Siberian ginseng) increased the serum concentration of digoxin, but did not alter the pharmacokinetics of dextromethorphan and alprazolam in humans. *Hypericum perforatum* (hypericum; St John's wort) decreased the blood concentrations of ciclosporin (cyclosporin), midazolam, tacrolimus, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline, but did not alter the pharmacokinetics of carbamazepine, pravastatin, mycophenolate mofetil and dextromethorphan. Cases have been reported where decreased ciclosporin concentrations led to organ rejection. Hypericum also caused breakthrough bleeding and unplanned pregnancies when used concomitantly with oral contraceptives. It also caused serotonin syndrome when used in combination with selective serotonin reuptake inhibitors (e.g. sertraline and paroxetine).

In conclusion, interactions between herbal medicines and prescribed drugs can occur and may lead to serious clinical consequences. There are other theoretical interactions indicated by preclinical data. Both pharmacokinetic and/or pharmacodynamic mechanisms have been considered to play a role in these interactions, although the underlying mechanisms for the altered drug effects and/or concentrations by concomitant herbal medicines are yet to be determined. The clinical importance of herb-drug interactions depends on many factors associated with the particular herb, drug and patient. Herbs should be appropriately labeled to alert consumers to potential interactions when concomitantly used with drugs, and to recommend a consultation with their general practitioners and other medical carers.

Botanical products are becoming increasingly popular as alternative medicines and an estimated one-third of adults in the developed countries use alternative therapies, including herbs. Herbs are often administered in combination with therapeutic drugs, raising the potential of pharmacokinetic and/or pharmacodynamic herb-drug interactions. Combined use of herbs with drugs may mimic, increase or reduce the effects of either component, resulting in clinically important herb-drug interactions.[1-4] Synergistic or additive therapeutic effects may lead to unfavourable toxicities and complicate the dosage regimen of long-term medications, while antagonistic interactions will result in decreased efficacy and therapeutic failure. The potential interaction of herbal medicines with drugs is a major safety concern, especially for drugs with narrow therapeutic indices (e.g. warfarin and digoxin)[5] and may lead to adverse reactions that are sometimes life threatening.[6]

Pharmacokinetic herb-drug interactions are as a result of altered absorption, metabolism, distribution and excretion of drugs. The underlying mechanisms for the altered drug concentrations by concomitant herbal medicines need to be identified, but the in-

duction or inhibition of hepatic and intestinal drug-metabolising enzymes (e.g. cytochrome P450 [CYP]) and/or drug transporters such as P-glycoprotein (P-gp) have been suggested.[7-11] Herbs are often given orally and, thus, herbal constituents may modulate gastrointestinal pH and motility. Because of high concentrations in the gut lumen, herbal constituents are likely to exert a major effect on intestinal enterocytes. These cells represent the first cell lining limiting entry of orally administered drugs into the body. Both P-gp and CYP3A4 are expressed at high levels in the villus tip of enterocytes, the primary site of absorption for orally administered drugs. The interplay of both intestinal P-gp and CYP3A4 determines bioavailability of many drugs such as ciclosporin (cyclosporin),[12] midazolam,[13] protease inhibitors,[14] verapamil,[15] digoxin[16] and talinolol.[17] Thus, the modulation of intestinal P-gp and CYP3A4 represents an important mechanism for the enhanced or reduced bioavailability of coadministered drugs.

There are increased numbers of reports on herb-drug interactions, although many of them are case reports and limited clinical observations. Thus, herb-drug interactions may be significantly under-reported and underestimated, and occur more frequently than drug-drug interactions. The reasons for this can be summarised as follows.

- Most patients (70%) do not reveal their herbal use to their allopathic practitioners.[18]
- Herbs have been used on a traditional basis, and rigorous preclinical and clinical assessments are not required by regulatory authorities.
- Most clinical trials of herbs have limited value, because of poor design, small sample size and, above all, use of poorly defined products of uncertain composition and consistency because of the lack of good quality control.[19]
- There is no comprehensive surveillance system for monitoring the adverse effects of herbs and herb-drug interactions in many countries.[20]
- A single herb usually contains a number of bioactive components, each of which may to a varying degree contribute to its pharmacological effects and drug interactions, leading to difficulties in predicting and exploring the mechanisms underlying observed herb-drug interactions.

We have reviewed the literature to identify reported interactions between herbal medicines and prescribed drugs from clinical studies. Literature searches were performed using the following databases: MEDLINE (via PubMed), Biological Abstracts, Cochrane Library, AMED (Allied and Complementary Medicine), Biosis Previews and EMBASE (all from their inception to March 2005). Extensive literature searches were also made using eight major reference books on herbal medicine,[21-28] 14 recently published reviews on herb-drug interactions[1-4,9,29-37] and our own extensive files and herbal database. In addition, a number of Chinese journals that publish studies on herbal medicines were hand searched from the first publication date onwards. These included *Yaoxue Xuebao* (*Chinese Pharmaceutical Bulletin*), *Zhonghua Yaolixue Yu Dulixue Zazhi* (*Chinese Journal of Pharmacology and Toxicology*), *Zhongcaoyao Zazhi* (*Chinese Journal of Planta Medica*), *Zhonghua Lekezazhi* (*Chinese Journal of Internal Medicine*), *Zhonghua Yixue Zazhi* (*Chinese Medical Journal*), *Zhongyi Zazhi* (*Journal of Traditional Chinese Medicine*), *Zhongguo Zhongcaiyao* (*Planta Medic Sinica*), *Zhongguo Zhongyao Zazhi* (*Chinese Journal of Materia Medica*) and *Zhonghua Zhongxiyi Jehe Zazhi* (*Chinese Journal of Integrated Traditional and Western Medicine*). The search terms used included herbal medicine, botanical drug, plant, phytotherapy, in combination with drug interactions, side effects, pharmacokinetics and pharmacodynamics. Once the herb that has been reported to interact with drugs in animals and/or humans was initially identified, a further detailed literature search for that herb was made to identify its potential interactions with drugs. Studies in humans including case reports, case series, clinical trials or other types of studies were all included and emphasised, whereas data from animal and *in vitro* studies were generally excluded except for those exploring the mechanisms for herb-drug interactions.

1. *Allium sativum* (Garlic)

Allium sativum (garlic), a widely used medicinal herb, is reported to have antimicrobial and immune-enhancing effects.[38,39] It is one of the herbal supplements most commonly used by HIV-infected patients to improve health and to treat some opportunistic infections.[40] Garlic contains high-level sulphur-containing compounds (e.g. allicin and alliin), numerous flavonoids/isoflavonoids (such as nobiletin, quercetin, rutoside [rutin] and tangeretin), polysaccharides, prostaglandins, saponins and terpenes (such as citral, geraniol, linalool, and α- and β-phellandrene).[41,42] Organosulfur compounds in garlic are believed responsible for its beneficial biological effects, but other compounds, such as S-allylcysteine, S-allylmercaptocysteine and *N*-α-fructosyl arginine, may also play a role.[43]

1.1 Dextromethorphan, Alprazolam and Midazolam

A recent study evaluated the effect of garlic extract on the metabolism and excretion of dextromethorphan (CYP2D6) and alprazolam (CYP3A4) in healthy volunteers (n = 14; 9 men and 5 women).[44] Treatment with a garlic extract (with an allicin potential of 600μg, alliin 1.5mg and *S*-allyl-L-cysteine 0.03mg in each 600mg tablet, 3 × 600mg twice daily) for 14 days insignificantly increased the ratio of dextromethorphan to its metabolite from 0.044 at baseline to 0.052 ($p > 0.05$). For alprazolam, there were no significant differences in pharmacokinetic parameters (maximum plasma concentration [C_{max}], area under the plasma concentration-time curve [AUC] and elimination half-life [$t_{½β}$]) at baseline and after garlic extract treatment. These results are in agreement with those of Gurley et al.,[45] who reported that supplementation with garlic oil did not alter the activity of CYP3A4 using midazolam as a probe in healthy volunteers. As garlic oil is generally devoid of alliin and allicin, it appears that both garlic capsule and oil are unlikely to alter the disposition of coadministered drugs that are primarily eliminated by CYP2D6- or CYP3A4-mediated metabolism. On the other hand, administration of garlic oil to healthy volunteers for 28 days reduced CYP2E1 activity by 39% when chlorzoxazone was used as a probe.[45]

In vitro and animal studies have indicated that the modulation of CYP enzyme activity and expression are dependent on the type and chemical composition of garlic supplements and dosage regimen. For example, a single dose of garlic oil in the rat resulted in a significant inhibition of hepatic CYP-catalysed reactions including aminopyrine *N*-demethylase (CYP2C) and aniline hydroxylase (CYP2E1) activity, but administration of garlic for 5 days led to a significant increase in these hepatic CYP activities.[46] The extracts from fresh and aged garlic inhibited CYP3A4 in human liver microsomes, and complementary DNA (cDNA)-expressed CYP2C9, CYP2C19, CYP3A4, CYP3A5 and CYP3A7 activities.[47]

1.2 Saquinavir and Ritonavir

In healthy volunteers (n = 10; 4 men and 6 women), a 3-week administration of garlic caplets (each caplet containing 3.6mg of garlic powdered extract) two times daily decreased the plasma AUC by 51%, trough plasma concentration at 8 hours (C_{8h}) by 49% and C_{max} by 54% of the protease inhibitor saquinavir.[48] Garlic caplets did not increase the toxicity of saquinavir. The altered pharmacokinetics of saquinavir were considered to be due to decreased bioavailability of saquinavir, rather than impairment of absorption or increased systemic clearance, as there was a similarity in the magnitude of the decrease in AUC, C_{8h} and C_{max}. The interaction may be caused by induction of P-gp in the gut mucosa, resulting in diminished bioavailability of saquinavir, which is a known substrate of CYP3A4[46] and P-gp.[49] Interestingly, a recent study found that raw garlic and garlic products inhibited the activities of P-gp *in vitro*, although the inhibition was low or moderate as compared with the known potent P-gp inhibitor verapamil.[47] It appears that the potential of CYP3A4 induction by garlic extracts is minimal; Markowitz et al.[44] and Gurley et al.[45] reported that neither garlic extract capsule nor oil modulated the activity of CYP3A4

when alprazolam and midazolam were used as probes.

The study by Piscitelli et al.[48] also found that the AUC, C_{8h} and C_{max} of saquinavir did not return to baseline values (only 60–70%) after the 10-day washout period. The mechanism for this is unknown, but it is suggested that garlic may undergo metabolism, resulting in metabolites that have a long half-life and enzyme-inducing properties. Alternatively, long-term use of garlic may lead to the formation and accumulation of saquinavir metabolite(s) that induce saquinavir metabolism. This may explain why some patients demonstrated a delay in the reduction of their saquinavir concentrations.[48] Decreases in exposure to saquinavir during long-term use have been demonstrated in HIV-infected patients.[50]

Interestingly, administration of two garlic capsules (10mg of natural source odourless garlic extract) for 4 days in healthy volunteers (n = 10; 5 men and 5 women) insignificantly decreased the AUC of the HIV-1 protease inhibitor ritonavir (400mg, single dose) by 17% and did not alter the C_{max}.[51] The reason for the discrepancy in the interaction of garlic and saquinavir or ritonavir is unclear. Ritonavir is a substrate of CYP3A4 and P-gp, and both an inhibitor and inducer of CYP;[52] therefore, a single dose does not reflect concentrations at steady state and, thus, affect the interaction outcomes. The lack of marked pharmacokinetic interaction could result from a transitory effect of induction and inhibition on the various drug disposition pathways of ritonavir. The lack of remarkable interaction is most probably a result of the short duration of garlic administration, and a longer duration of garlic therapy may be required for a significant decrease in ritonavir plasma concentrations.

However, there was a case report by Laroche et al.[53] in which two HIV-infected patients taking garlic supplements for >2 weeks developed severe gastrointestinal toxicity after beginning ritonavir-containing antiretroviral therapy (400 or 600mg twice daily). The symptoms resolved after discontinuing garlic or ritonavir. This was not likely to be related to increased systemic concentrations of ritonavir. Gastrointestinal symptoms recurred during rechallenge with low-dose ritonavir (100mg twice daily) in the presence of garlic.[53] The observed toxicity could have been due to ritonavir inhibiting or inducing the metabolism of garlic constituents, resulting in toxic compounds from garlic. In addition, garlic constituents may inhibit the CYP3A-mediated metabolism or P-gp-mediated transport of ritonavir, leading to increased ritonavir concentrations. The effect of garlic may be less after multiple doses than after a single dose of ritonavir, as ritonavir undergoes autoinduction during the first 2 weeks of therapy,[50] potentially minimising the effects of further induction. Further studies are required to explore the effects of garlic supplements (particularly for long-term use) on the pharmacokinetics and pharmacodynamics of ritonavir.

Since garlic has been most commonly used as a dietary supplement in patients infected with HIV,[54,55] it is necessary to advise patients on the potential detrimental effect of garlic when coadministered with protease inhibitors such as saquinavir and ritonavir. Patients receiving anti-HIV therapy containing saquinavir should avoid using garlic supplements. It would be interesting to investigate whether enhanced pharmacokinetics caused by potent inhibitors of CYP3A such as ritonavir can prevent garlic-induced alterations in saquinavir concentrations.

1.3 Warfarin

Two case reports suggested the combination of warfarin and garlic extract caused an increase of clotting time and international normalised ratio (INR).[56,57] There were case reports that garlic could cause postoperative bleeding[58,59] and spontaneous spinal epidural haematoma.[60,61] The additive effect is considered to be because some garlic components have an anticoagulant effect and, thus, enhanced the effect of warfarin. Certain organosulfur components have been shown to inhibit human platelet aggregation *in vitro* and *in vivo*.[62-65] This effect is beneficial for the cardiovascular system; however, garlic should be stopped in patients 4–8 weeks prior to an

operation or in those receiving long-term administration of warfarin.

1.4 Chlorpropamide

Garlic may also enhance the effect of antihyperglycaemic drugs. A woman who ate a curry containing garlic and *Momordica charantia* (karela, bitter melon) while on chlorpropamide therapy experienced an enhanced antihyperglycaemic response.[66] Garlic extracts have been known to produce antihyperglycaemic effects in animals[67-69] and humans,[70,71] providing an explanation for garlic-chlorpropamide interaction. However, bitter melon also has an antihyperglycaemic effect in streptozotocin-induced diabetic mice[72] and may contribute to the interaction.

1.5 Paracetamol (Acetaminophen)

Administration of commercial aged garlic extract (approximately equivalent to six to seven cloves of garlic) for 3 months in healthy volunteers (n = 16) did not alter the oxidative and glucuronidation metabolism of paracetamol (acetaminophen) 1g orally, but caused a slight increase in sulfation.[73] However, a study in mice indicated that diallyl sulfone ($DASO_2$) derived from garlic decreased the plasma concentrations of oxidative paracetamol metabolites, but not nonoxidative paracetamol metabolites.[74] This is considered to be as a result of the inhibition of CYP2E1, which is the major enzyme responsible for bioactivation of paracetamol.[75] In liver microsomes, diallyl sulfone significantly inhibited paracetamol oxidation to *N*-acetyl-p-benzoquinone imine (the toxic metabolite of paracetamol).[74] All these results provide an explanation for the protective effect of diallyl sulfone on paracetamol-induced hepatotoxicity.[74] When administered orally 1 hour prior to, immediately after or 20 minutes after a toxic dose of paracetamol, diallyl sulfone (25 mg/kg) completely protected mice from development of hepatotoxicity.[74] A protective effect was also observed when diallyl sulfone at a dose as low as 5 mg/kg was given to mice 1 hour prior to paracetamol administration.

2. *Angelica dahurica* (Baizhi)

Angelica dahurica (baizhi) is an important herbal medicine used in traditional Chinese medicine. Its root has been used primarily to treat headache caused by common cold, migraine, pain caused by swelling, contusions and strains, because of its anti-inflammatory, analgesic and antipyretic actions.[76,77] The major bioactive components in *A. dahurica* are furanocoumarins (e.g. imperatorin and isoimperatorin), coumarins and scopoletin.[78-80]

2.1 Preclinical Studies: Diazepam and Tolbutamide

Treatment of rats with *A. dahurica* extract (10 mg/kg intravenously) increased the C_{max} of diazepam by 4-fold, although other pharmacokinetic parameters such as AUC and clearance were not markedly altered.[81] This is because the elimination of diazepam (a high-clearance drug) is dependent on hepatic blood flow rate and the change of intrinsic clearance had little effect on its hepatic clearance. However, the first-pass effect of diazepam may be altered by the *A. dahurica* extract at high-dose, leading to an enhanced effect on the CNS. *A. dahurica* extract (1 g/kg) significantly increased the duration of rotarod test disruption following intravenous administration of diazepam.[81] Low-dose (0.3 g/kg) *A. dahurica* had no effect. In addition, some components from *A. dahurica* are modulators of benzodiazepine receptors.[82,83] Therefore, *A. dahurica* may modulate the effects of benzodiazepine receptor agonists such as diazepam as a result of both pharmacokinetic and pharmacodynamic interactions.

In addition, treatment of rats with *A. dahurica* extract (10 mg/kg intravenously) prolonged the half-life and decreased the clearance of tolbutamide intravenously administered.[81] This can be explained by the reduced liver intrinsic clearance due to CYP2E1 inhibition. *In vitro* and *in vivo* studies have found that *A. dahurica* extract and its furanocoumarins extensively inhibited various CYP isoenzymes, including CYP2E and CYP3A,[81,84-88] whereas treatment of rats with *A. dahurica Radix*

extract caused an inhibition of various CYP isoenzymes.[81]

3. *A. sinensis* (Danggui, Dong Quai)

A. sinensis, belonging to the Umbelliferae (now know as the Apiaceae) family, is also known as 'danggui' or 'dong quai' in traditional Chinese medicine.[89] Simple alkyl phthalides are the major components of the essential oil fraction of the *A. sinensis* roots. These include ligustilide, (Z)-liqustilide, (Z)-6,7-epoxyligustilide, angelicide, butylphthalide, (Z)-butylidenephthalide and 2,4-dihydrophthalic anhydride.[21,90-93] The non-volatile constituents are phenylpropanoids (e.g. (E)-ferulic acid), benzenoids (e.g. vanillic acid) and coumarins (e.g. angelol G, angelicone and umbelliferone).[91,94,95] *A. sinensis* root is used to treat gynaecological diseases, such as menopausal symptoms and menstrual irregularities, anaemia, constipation and bone injuries.[96-100] However, a randomised, placebo-controlled clinical study indicated that *A. sinensis* root (4.5 g/day) for 24 weeks did not alleviate menopausal symptoms.[101]

3.1 Warfarin

Although *A. sinensis* is a commonly used herbal medicine, there is a lack of clinical data on *A. sinesis*-drug interactions except for one case report. A 46-year-old African American woman with atrial fibrillation stabilised on warfarin experienced a >2-fold increase in prothrombin time and INR after taking *A. sinesis* concurrently for 4 weeks.[102] The increased INR may be explained by pharmacodynamic interactions rather than pharmacokinetic alterations. *A. sinesis* extract and its ingredient, ferulic acid, had been shown to inhibit rat platelet aggregation *in vivo*.[103] A study in rabbits also indicates that oral intake of *A. sinesis* root extract (2 g/kg twice daily) significantly decreased the prothrombin time when combined with warfarin (2 mg/kg), while the pharmacokinetics of warfarin were not altered.[104] However, *in vitro* studies have found that components from *A. sinensis* root can modulate CYP3A4 and CYP1A, indicating a potential of drug interactions with CYP substrates. For example, the decoction or infusion from *A. sinensis* root inhibited CYP3A4-catalysed testosterone 6β-hydroxylation in human liver microsomes,[88] whereas ferulic acid (0.5 μmol/L) from *A. sinensis* root significantly inhibited ethoxyresorufin *O*-deethylase and methoxyresorufin *O*-demethylase (CYP1A) activity.[90,105] Thus, *A. sinensis* may alter the metabolism of drugs that are predominantly eliminated by CYP3A or CYP1A. All of these results indicate that precautionary advice should be given to patients who self-medicate with *A. sinensis* root preparations while receiving long-term warfarin treatment; and well designed clinical studies are required to examine the effects of *A. sinensis* root on drugs such as warfarin and substrates of CYP3A4.

4. *Eleutheroccus senticosus* (Siberian Ginseng)

Siberian ginseng, the roots of *Eleutheroccus senticosus*, is among the ten most popular supplements used in the US.[106] It is a tonic or adaptogen that confers resistance to the effects of stress.[107,108] The eleutherosides are the major constituents of Siberian ginseng that have been given the most attention and are considered responsible for the proposed adaptogenic activity. Most commercially available extracts have been standardised according to the content of eleutheroside B (syringin 4-β-D-glucoside) and eleutheroside E (syringaresinol 4, 4' β-D-diglucoside). Other constituents with reported biological activities include sesamin, β-sitosterol, hedarasaponin B and isofraxidin, as well as various flavonoids and hydroxycinnamates.[107,109]

4.1 Alprazolam and Dextromethorphan

A recent clinical study in healthy volunteers investigated the effects of a standardised Siberian ginseng extract on the activity of CYP2D6 and CYP3A4 using probe substrates dextromethorphan and alprazolam, respectively. Treatment with Siberian ginseng (1 × 485mg twice daily) for 14 days did not alter the urinary dextromethorphan metabolic ratio or the pharmacokinetics of alprazolam,[110] indicating that Siberian ginseng does not significantly induce or inhibit CYP2D6 and CYP3A4. This is

consistent with the result from an *in vitro* study where the extracts of Siberian ginseng did not inhibit the activity of human CYP3A4 using cDNA-expressed human liver microsomes.[111] However, Siberian ginseng extract inhibited mouse hexobarbital metabolism *in vitro*[112] and administration of Siberian ginseng extract to mice in the short- (40–320 mg/kg intraperitoneally × 1 day) or long-term (80–320 mg/kg intraperitoneally × 4–5 days) potentiated the sedative effect of hexobarbital with decreased sleep latency and increased sleep duration.[112] As hexobarbital is mainly metabolised by CYP2C9,[113] the interaction may involve CYP2C9 induction by Siberian ginseng.

4.2 Digoxin

A 74-year-old man taking a constant dose of digoxin for many years was found to have an increased serum digoxin concentration, but without signs of toxic effects.[114] Common causes of elevated serum digoxin were ruled out and the patient's serum digoxin concentration remained high after digoxin therapy was stopped. The patient then revealed that he was taking Siberian ginseng. The patient stopped taking the herb and the serum digoxin concentration soon returned to an acceptable level. Digoxin therapy was then resumed. The patient resumed taking ginseng several months later and the serum digoxin concentration rose again. The ginseng was stopped once more and the serum digoxin concentrations again returned to within the therapeutic range. A recent study indicated that Siberian ginseng contained some digoxin-like constituents, interfering with digoxin serum assay results. With the fluorescence polarisation immunoassay, apparent digoxin activity has been observed in Siberian ginseng preparations.[115]

5. *Ginkgo biloba* (Ginkgo)

Ginkgo biloba leaf extract (ginkgo) is one of the most popular herbal medicines in the world because of its purported, but unproven, beneficial effects, including memory-enhancing, cognition-improving and antiplatelet effects.[116-122] Most clinical studies on efficacy and safety of ginkgo have been conducted with a standardised aqueous acetone extract, EGB 761, which is in solid form. The primary constituents of ginkgo include flavonoids (e.g. kaempferol), terpenoids (e.g. ginkgolides and bilobalaides) and organic acids (e.g. ginkgolic acids and alkylphenols).[123-127] The latter have been associated with adverse events such as allergy, induction of neurons, genotoxicity and other toxicities.[127-131] Thus, ginkgolic acids are restricted in EGB 761 to 5 parts per million (ppm).

5.1 Trazodone

An 80-year-old women with Alzheimer's disease fell into coma when taking a low dose of the atypical antidepressant trazodone in conjunction with ginkgo.[132] The mechanism of this is unclear but it may be associated with enhanced GABA-related neuronal activity in the brain by ginkgo. Bilobalide in ginkgo significantly increased GABA levels and glutamic acid decarboxylase in mouse brain,[133] and prevented the reduction of GABA levels and glutamic acid decarboxylase activity induced by 4-*O*-methylpyridoxine in mouse hippocampus.[134] In addition, ginkgo may increase CYP3A4 activity, leading to increased formation of the active metabolite of trazodone, *m*-chlorophenylpiperazine. Feeding of rats with ginkgo extract (0.5% w/w) for 4 weeks markedly increased the total content of CYP in a dose- and time-dependent manner, and the hepatic levels of CYP2B1, 2B2, CYP3A1 and 3A2 messenger RNA (mRNA).[135,136] Additionally, treatment of mice with bilobalide 30 mg/kg/day for 4 days increased hepatic 7-methoxycoumarin *O*-demethylase activity.[137] However, oral administration of ginkgo 60mg four times daily for 28 days to healthy volunteers (n = 12) did not alter the activity of CYP1A2, CYP2E1, CYP3D6 and CYP3A4 when caffeine, chlorzoxazone, debrisoquin and midazolam, respectively, were used as probe drugs.[45]

5.2 Warfarin, Aspirin (Acetylsalicylic Acid) and Ibuprofen

Ginkgo may interact with warfarin, as a few case reports associated concomitant use of ginkgo extract with warfarin with the development of intracerebral

haemorrhage.[138,139] There is a case report on spontaneous hyphaema when ginkgo extract was combined with aspirin (acetylsalicylic acid).[140] Additionally, there is a case report on fatal intracerebral mass bleeding associated with the combined use of ginkgo extract and ibuprofen.[141] However, a recently published randomised, double-blind, placebo-controlled crossover study indicated that oral ingestion of ginkgo extract (100mg daily for 4 weeks) did not alter the INR in 24 Danish outpatients (14 women and 10 men) on stable, long-term warfarin treatment, and the geometric mean dosage of warfarin did not change during the treatment periods.[142] It appears that many factors associated with the source of ginkgo extract, dosage regimen and patients influence the clinical outcomes when combined with warfarin.

In addition, ginkgo extract enhanced the antiplatelet and antithrombotic effects of ticlopidine in normal and thrombosis-induced rats, resulting in prolonged bleeding times by 150%.[143] Therefore, concomitant use with warfarin, aspirin or any other anticoagulants such as ticlopidine and heparin is ill advised.

The mechanism for these interactions is unknown. Both pharmacokinetic and pharmacodynamic mechanisms may be involved, given that ginkgo extracts can modulate various CYP isoenzymes[135,137] and exert antiplatelet activity.[144] Ginkgolides are potent inhibitors of platelet-activating factor.[144] There are case reports of postoperative bleeding[145] and spontaneous haemorrhage[146-148] caused by ginkgo consumption. However, a prospective, double-blind, randomised, placebo-controlled study in 32 young, healthy male volunteers indicated that oral treatment with ginkgo extract (EGb 761) at 120, 240 or 480 mg/day for 14 days did not alter platelet function or coagulation.[149] It appeared that bleeding caused by ginkgo often occurred in the elderly or postoperative patients who might have impaired platelet function before the use of ginkgo.

5.3 Digoxin

An open-label, randomised, crossover study in eight healthy volunteers indicated that oral treatment of commercial ginkgo extract at 80mg three times daily for 2 weeks increased the AUC of digoxin 0.5mg by 21.9% ($p > 0.05$).[150] There was no significant difference in C_{max}, half-life or plasma clearance of digoxin between the groups. However, careful therapeutic drug monitoring is a necessity when digoxin is combined with ginkgo used for a long period.

5.4 Omeprazole

In a recent clinical study involving 18 healthy Chinese volunteers, treatment with ginkgo (140mg twice daily) for 12 days significantly decreased the plasma concentrations of omeprazole and its sulfone conjugate, while the 5-hydroxyomeprazole concentration was significantly increased.[151] A significant decrease in the ratio of omeprazole AUC to 5-hydroxyomeprazole was observed in poor and extensive metabolisers with regard to *CYP2C19* genotype, with the decrease greater in poor metabolisers than extensive metabolisers.[151] No significant changes in the AUC ratios of omeprazole to its sulfone conjugate were observed. These results indicate that ginkgo is able to induce CYP2C19 and, thus, enhance omeprazole hydroxylation in a CYP2C19 genotype-dependent manner. Caution should be used when patients concomitantly take ginkgo and CYP2C19 substrates.

5.5 Antihypertensive Agents

Increased blood pressure was observed in an elderly patient who took a thiazide diuretic and ginkgo for hypertension.[20] Metabolic inhibition of the thiazide diuretic by ginkgo is a possible mechanism. Treatment with ginkgo for 4 weeks significantly reduced the hypotensive effect of nicardipine that is metabolised by CYP3A2 in rats.[135]

A single oral treatment of rats with ginkgo leaf extract (20 mg/kg) significantly decreased the terminal elimination rate constant and increased the mean residence time of diltiazem (3 mg/kg).[152] It also

significantly increased the AUC and absolute bioavailability of diltiazem after oral administration (30 mg/kg). These effects of ginkgo leaf extract on the pharmacokinetics of diltiazem, a typical CYP3A4 probe, were considered to be due to the inhibition of intestinal and hepatic CYP3A4. The addition of ginkgo leaf extract to small intestine and liver microsomes inhibited the CYP3A4-mediated formation of *N*-demethyl diltiazem with a concentration that produces 50% inhibition (IC_{50}) of 50–182 μg/mL. This inhibition appeared to be caused, at least in part, by a mechanism-based inhibition. A single oral pretreatment with ginkgo leaf extract (20 mg/kg) decreased transiently the rate of formation of *N*-demethyl diltiazem and total amount of CYP in intestinal or hepatic microsomes.[152]

Treatment with ginkgo leaf extract at commonly used dose (120mg) for 7 days did not alter blood pressure in healthy volunteers,[153,154] but it reduced stress-induced rise in blood pressure without affecting the heart rate.[155] Conversely, long-term (>3 month) ingestion of ginkgo reduced blood pressure in humans.[156] ginkgo also decreased blood pressure in spontaneously hypertensive rats [157] and attenuated the development of hypertension in experimental hypertensive rats.[158] Thus, ginkgo is a potent peripheral vasodilator.[120]

5.6 CNS Drugs

Although oral administration of ginkgo (60mg four times daily for 28 days) did not alter the metabolism of midazolam in healthy volunteers (n = 12),[45] ginkgo may modulate the benzodiazepine receptor, raising the potential of interaction with benzodiazepines. Single administrations of ginkgo leaf extract (8–16 mg/kg intraperitoneally or 48 or 96 mg/kg/day orally) for 8 days in rats significantly decreased social contact under conditions that did not influence locomotor activity, whereas diazepam (1 mg/kg intraperitoneally) significantly increased social contact.[159] The combination of diazepam with oral ginkgo increased social interaction to an extent greater than observed with diazepam alone.[159] It appears that these effects may be mediated by interactions with certain sites of central GABA, benzodiazepine and chloride ion channel receptor complexes.

Donepezil is a cholinesterase inhibitor used in the management of Alzheimer's disease.[160] Treatment of 14 patients with Alzheimer's disease with ginkgo extract at a dosage of 90 mg/day for 30 days did not significantly alter the plasma concentration of donepezil or red blood cell cholinesterase activity.[161] In addition, ginkgo supplementation did not change the cognitive function of patients throughout the study. Donepezil is metabolised by CYP3A4 and CYP2D6,[162] and theoretically ginkgo as a CYP3A4 inducer may have an impact on donepezil clearance. A lack of ginkgo-donepezil interaction could be due to the modulating effect of ginkgo on intestinal donepezil absorption and renal clearance. Although this study indicates that ginkgo does not have a major impact on the pharmacokinetics and therapeutic response of donepezil, further studies are needed to identify the effect of ginkgo on other CYP3A4 substrate drugs.

The ginkgo leaf and seed contain a low level of ginkgotoxin (4'-*O*-methylpyridoxine), which is a neurotoxin capable of inducing convulsion, and reducing GABA levels and glutamic acid decarboxylase activity in the hippocampus.[134,137,163,164] Thus, ginkgotoxin may enhance the effectiveness of administered antiepileptic drugs (e.g. carbamazepine, phenytoin and phenobarbital [phenobarbitone]). It would be prudent to avoid the use of ginkgo in known epileptic patients. Additionally, concomitant use with medications known to decrease seizure threshold, such as tricyclic antidepressants, would be ill advised.

Ginkgo may enhance the efficiency and reduce the extrapyramidal adverse effects of the classic antipsychotic haloperidol in patients with schizophrenia, especially on their positive symptoms.[165,166] The antioxidant effect of ginkgo is a possible mechanism, as the combination decreased blood superoxide dismutase levels in these patients.[165] Other mechanisms such as modulation of GABA receptors in the brain[133,134] may also be involved.

5.7 Antihyperglycaemics

Ingestion of ginkgo extract 120mg daily for 3 months by healthy glucose-tolerant individuals caused a significant increase in pancreatic β-cell insulin and C-peptide response.[156] However, the same treatment decreased the AUC of plasma insulin by 26% in hyperinsulinaemic patients with type 2 diabetes mellitus taking oral antihyperglycaemic medications.[167] It appears that ginkgo extract may increase the hepatic metabolic clearance rate of not only insulin but also the antihyperglycaemic agents in diabetic patients, resulting in reduced insulin-mediated glucose metabolism and elevated blood glucose. In aged rats, pretreatment with a 0.1% ginkgo extract diet for 5 days significantly attenuated the antihyperglycaemic action of tolbutamide with enhanced activity of (*S*)-warfarin 7-hydroxylase (CYP2C9), which is also a major CYP isoenzyme metabolising tolbutamide.[168] A clinical study documenting the interaction of antihyperglycaemic drugs and ginkgo is needed.

6. *Glycyrrhiza glabra* (Licorice)

Glycyrrhiza glabra (licorice) is a common herb in Chinese traditional medicine and used as a major component in Japanese herbal medicines such as Xiao Chai Hu Tang (Shosaiko-to in Japanese). Licorice contains glycyrrhizin (glycyrrhizic acid, a glycoside 50 times sweeter than sugar), oleane triterpenoids, glucose, ammonia, polyphenols, flavonoids and sucrose.[169,170] Glycyrrhizin is hydrolysed by intestinal microflora to the pharmacologically active form, glycyrrhetic acid. Xiao Chai Hu Tang contains rich flavonoids such as liquiritigenin, baicalein, wogonin and oroxylin A.[171]

6.1 Midazolam

In a crossover study in healthy volunteers, oral ingestion of aqueous licorice extract for 7 days did not significantly alter the pharmacokinetic parameters and sedative effects of midazolam.[172] Midazolam is a typical substrate of CYP3A4.[173] Ethanolic extracts of licorice inhibited CYP3A4-mediated metabolism of benzyloxyresorufin in human liver microsomes.[111] *In vitro* study indicated that glabridin, an isoflavone derived from licorice root, inactivated CYP3A4 and CYP2B6 in a time- and concentration-dependent manner, but CYP2C9 was competitively inhibited by glabridin.[174] The repeated exposure of licorice root extract or glycyrrhizin also increased the metabolism of CYP3A4 substrates and induced the expression of CYP3A at protein and mRNA levels in the mouse.[175] The discrepancy between *in vitro* and animal and human studies may reflect the importance of herbal dosage and regimen as influencing factors in the modulation of CYP isoenzymes.

6.2 Corticosteroid: Prednisolone

Homma et al.[176] compared the effect of three traditional Chinese medicines, Sho-saiko-To, Saiboku-To and Sairei-To, on the pharmacokinetics of prednisolone in healthy volunteers. All of these herbal medicines consisted of similar herbal prescriptions containing equal contents of glycyrrhizin. All subjects received a single oral dose of prednisolone 10mg before oral treatment with one of the herbal preparations. After a 2-week wash-out interval, each subject received one of the test herbal preparations for 3 days at daily doses of 7.5 or 9.0g. On the third study day, prednisolone 10mg was administered orally in combination with the test herbal preparation. Treatment of Sho-saiko-To resulted in a significant decrease in serum prednisolone AUC by 17.2%, while Saiboku-To treatment significantly increased the AUC by 15.2%. Sairei-To treatment did not alter the AUC. Consistently, the AUC ratios of prednisone over prednisolone, which reflect the 11 β-hydroxysteroid dehydrogenase activity, increased in the Sho-saiko-To group ($p < 0.01$), decreased in the Saiboku-To group ($p < 0.01$), but did not change in the Sairei-To group.[176] The differential effect of the three herbal preparations on 11 β-hydroxysteroid dehydrogenase activity indicated the existence of unknown modifiers of steroid metabolic enzymes. It would be interesting to examine the effect of licorice used as a single agent on the concentrations of corticosteroids in humans.

Both glycyrrhizin and glycyrrhetic acid are potent inhibitors of 5α-, 5β-reductase and 11β-dehydrogenase.[177,178] The inhibition of these enzymes may result in a decrease in the inactivation of steroids and, thus, may modulate the effects of endogenous and administered steroids.[179] An *in vitro* study found that 11β-dehydrogenase in skin from nude mice was inhibited by glycyrrhetinic acid and potentiated the action of hydrocortisone.[180] Carbenoxolone sodium (a chemical derivative of licorice) enhanced the renal effect of corticosterone and cortisol on sodium and potassium in adrenalectomised male rats.[181] Xiao Chai Hu Tang decreased the plasma AUC of prednisolone,[176] whereas Saiboku-To increased the AUC in rat studies. All of these herbal mixtures contain glycyrrhizin and many other components that may exert inhibitory or stimulatory effects on 11β-dehydrogenase.

A recent case report described a patient who experienced life-threatening hypokalaemic paralysis caused by consumption of licorice in the form of a tea sweetener superimposed on long-term consumption of licorice candy.[182] Lin et al.[183] reported another case where an elderly Asian man taking licorice long-term experienced hypokalaemic paralysis. It is unclear whether the hypokalaemic paralysis is related to the enzyme inhibition. Thus, human studies are required to explore the effects of licorice components (in particular glycyrrhizin and glycyrrhetic acid) on plasma concentrations of corticosteroids and possible pharmacodynamic consequence.

6.3 Preclinical Study: Tolbutamide

Pretreatment of rats with Xiao Chai Hu Tang 250 mg/kg decreased the plasma concentration of tolbutamide.[184] Xiao Chai Hu Tang inhibited the gastric emptying rate and increased intragastric pH,[184,185] which may contribute to the interaction with tolbutamide.[185] It is unclear whether Xiao Chai Hu Tang induces CYP2C9 and, thus, enhances the hepatic clearance of tolbutamide.

7. *Hypericum perforatum* (St John's Wort)

Hypericum perforatum (hypericum; St John's wort) is one of the most commonly used herbal medicines for the treatment of depression.[186] Hypericum is a complex mixture of over two dozen constituents, including flavonols, flavonol glycosides, biflavones, naphthodianthrones, acylphloroglucinols and phenylpropanes.[187,188] Among these, hyperforin is the major constituent responsible for its antidepressant activity, as it inhibits the reuptake of neurotransmitters (e.g. serotonin, norepinephrine and dopamine) in synapses.[189] The bioavailability of hypericin and pseudohypericin in humans appears to be about 15% and 20%, respectively.[190,191] Because of the extensive use and concern of drug interactions, the effects of hypericum on the pharmacokinetics and pharmacodynamics of some clinically important drugs have been investigated clinically. In addition, spontaneous reports and published case reports provide supportive evidence for the interactions of hypericum with certain drugs.

7.1 Amitriptyline

Hypericum and amitriptyline have a high probability of concomitant use. Concomitant intake of the hypericum extract LI 160 (900mg daily) for at least 2 weeks in 12 depressed patients decreased the AUC of amitriptyline by 22% and nortriptyline (demethylated metabolite) by 41%, as well as of all hydroxylated metabolites, except for 10-E-hydroxy-nortriptyline.[192] Plasma concentrations of amitriptyline and hydroxylated metabolites gradually decreased, whereas nortriptyline concentrations were already markedly decreased after 3 days of co-treatment with hypericum. Cumulative urinary amounts of amitriptyline and metabolites decreased to the same extent as plasma concentrations upon hypericum comedication. The demethylation of amitriptyline to nortriptyline is primarily catalysed by CYP2C19 and CYP3A4.[193,194] The further metabolism of nortriptyline through hydroxylation at the 10-position is mediated by CYP3A4 and CYP2D6.[195] Thus, induction of CYP3A4 may have

caused the decrease in the AUC of amitriptyline and nortriptyline. Physicians should be aware of this interaction when treating patients with amitriptyline.

7.2 Benzodiazepines: Alprazolam and Midazolam

Both alprazolam[196] and midazolam[173] are metabolised by CYP3A4. Short-term ingestion (900 mg/day for 1–3 days) of hypericum did not alter the pharmacokinetics of alprazolam[197] and midazolam[198] in healthy volunteers (n = 12; 5 female, 7 male). However, long-term administration of hypericum (900 mg/day for 2 weeks) significantly increased the oral clearance of midazolam by 108.9% and decreased the oral bioavailability by 39.3%.[198] In contrast with the >50% decrease in the AUC when midazolam was administered orally, long-term hypericum administration caused a 20% decrease in AUC when midazolam was given intravenously.[198] Similarly, when hypericum was administered for 12[199] or 28 days,[45] the clearance of midazolam was significantly enhanced.

7.3 Carbamazepine

Intake of hypericum 900 mg/day for 2 weeks did not alter the pharmacokinetics of the antiepileptic drug carbamazepine in healthy volunteers.[200] Carbamazepine is mostly metabolised by CYP3A4.[201] The predominant enzyme catalysing the metabolism of carbamazepine is CYP3A4, but other enzymes such as CYP2C8 also make a substantial contribution.[202] The lack of alteration of the pharmacokinetics of carbamazepine by hypericum may be due to the presence of both CYP-inducing and -inhibiting constituents in the same formulation, the inducing effects of carbamazepine on multiple CYP isoenzymes[203,204] and that carbamazepine is not a substrate for P-gp.[205] It should be noted that another widely used herb, Saiko-ka-ryukotsu-borei-to extract powder, did not affect the pharmacokinetics of carbamazepine in rats.[206]

7.4 Ciclosporin (Cyclosporin)

Ciclosporin is a widely used standard immunosuppressive agent in transplantation and is also used in the treatment of various autoimmune diseases. It has a narrow therapeutic index,[207] with allograft rejection occurring when blood concentrations fall below the effective concentration.[207] Ciclosporin is a substrate of P-gp[208] and CYP3A4.[209-212] The drug undergoes extensive CYP3A4-mediated biotransformation to >30 metabolites that differ in their therapeutic activity and toxicity.[213] Ciclosporin and its metabolites are mainly eliminated into the bile,[214] with 96% of an oral dose recovered in faeces and <0.1% of the parent drug eliminated unchanged.[215] Therefore, the induction of both CYP3A4 and P-gp by hypericum components may act to reduce the plasma concentration of ciclosporin to subtherapeutic levels, leading to clinically significant consequences such as the rejection of a transplanted organ.

A few case reports of interactions between ciclosporin and hypericum have been published.[216-219] These published case reports concerned patients who received transplantation of heart (n = 2), liver (n = 1), kidney (n = 1) and pancreas (n = 1). Decreased blood trough concentrations of ciclosporin had been observed and this was associated with transplant graft rejection observed in all of these cases. The decrease in ciclosporin concentrations ranged from 25%[217] to 62%[216] within 3–4 weeks of initiating usage of hypericum. Some of the patients recovered spontaneously after stopping the herbal medicine, while others needed an increased ciclosporin dose.

Thirty patients with kidney transplants using hypericum were found to have significantly decreased plasma ciclosporin concentrations by an average of 47% (range 33–62%).[220] This led to ciclosporin doses being increased by 46% (range 15–115%). When the herbal remedy was withdrawn, ciclosporin concentrations increased by a mean of 187% (range 84–292%) and the dose of ciclosporin was decreased to that taken before the intake of hypericum.

A recent study by Bauer et al.[221] reported that treatment with hypericum extract 600 mg/day for 2 weeks decreased the AUC, C_{max} and plasma trough concentration for ciclosporin by 41–46% in 11 renal transplant patients. Although the dose of hypericum used in this study (600 mg/day) was below that recommended for this formulation (900 mg/day), ciclosporin doses were increased by a median of 55.6% at day 15, with the first dose adjustment required only 3 days after initiation of hypericum treatment. The metabolite patterns of ciclosporin were also considerably altered during treatment of hypericum. AUC, C_{max} and trough concentration for AM1 and AM1c were significantly reduced by about 60%, an effect larger than the one observed for the parent compound. In contrast, the metabolites AM9 and AM19 remained unaffected by hypericum treatment. Renal function remained stable during hypericum treatment as indicated by serum creatinine and urea concentrations. Induction of CYP3A4 and P-gp are considered major mechanisms for the reduced plasma concentrations of ciclosporin. In healthy volunteers, pretreatment with hypericum for 12 days increased the clearance of ciclosporin by about 1.9-fold.[199] The induction of P-gp by hypericum may result in enhanced biliary excretion of those ciclosporin metabolites with higher affinities for P-gp, and they would also be less likely to be reabsorbed from the intestine. As a result, the enterohepatic cycle would be interrupted and blood concentrations of P-gp substrates would decrease.

7.5 Dextromethorphan

The antitussive drug dextromethorphan is routinely used as probe substrate[222] to evaluate the activity of polymorphic[223] CYP2D6 in humans. In a clinical study to evaluate the effect of hypericum intake on orally administered dextromethorphan, no interaction was evident when the drug was taken after 3 days exposure to the herb, at a dose of 900 mg/day, and continued during the sampling period.[197] The herbal preparation did not alter the metabolic ratio in the urine (ratio of dextromethorphan to the metabolite dextrorphan).

7.6 Digoxin

No significant alteration of the pharmacokinetics of digoxin was observed following a single dose of hypericum. However, a single-blind, placebo-controlled parallel study involving 25 healthy volunteers indicated that repeated intake of the herb at 900 mg/day for 10 days resulted in a decreased AUC by 25%, plasma C_{max} by 33% and concentration at the end of a dosing interval by 26%, with the decline in trough concentration becoming more pronounced as the duration of hypericum intake increased.[224] It is considered that the altered pharmacokinetics of digoxin by the herbal remedy is due to induction of P-gp following multiple-dose treatment with hypericum. This is because the $t_{1/2}\beta$ for digoxin elimination remained constant, but a reduction in C_{max} and AUC was observed as a result of altered absorption or distribution, rather than metabolism.

In fact, digoxin is not significantly metabolised by CYP isoenzymes in human hepatocytes and human liver microsomes.[225] However, in contrast with human microsomes, microsomal CYP3A proteins have been shown to catalyse the sequential oxidative cleavage of digoxin in rats.[226] In a subsequent clinical study, the administration of hypericum extract to eight healthy male volunteers over 14 days resulted in an 18% decrease of digoxin exposure after a single digoxin dose (0.5mg) and in 1.4-fold increased expression of duodenal P-gp.[227] Digoxin is a well known substrate of P-gp.[228,229] Other inducers of digoxin clearance such as rifampicin (rifampin)[16,230] and phenytoin[231] have been shown to decrease digoxin plasma concentration, mediated by P-gp. Flavonoids present in the hypericum may contribute to the activation of P-gp.[232] No spontaneous case reports of interactions between hypericum and digoxin have been identified.

7.7 Fexofenadine

Fexofenadine is a nonsedating antihistamine[233] used as a probe substrate for P-gp.[234,235] It does not undergo significant metabolic biotransformation, as 95% of the dose is excreted unchanged either in the urine or faeces after biliary excretion.[236] It is the

active metabolite of terfenadine, but has the advantage that it is not cardiotoxic and does not cause the rare but potentially fatal adverse reaction associated with certain drug interactions involving terfenadine.[237]

In healthy volunteers (n = 12; 9 women and 3 men), a single dose of hypericum (900mg) significantly increased the C_{max} of fexofenadine by 45% and significantly decreased the oral clearance by 20%, with no change in half-life or renal clearance.[238] However, long-term administration of hypericum (900mg for 2 weeks) caused a 35% decrease in C_{max} of fexofenadine and a 47% increase in oral clearance. In another clinical study in healthy volunteers, treatment of hypericum (900 mg/day) for 12 days also enhanced the oral clearance of fexofenadine by 1.6-fold.[199] It appears that a single dose of hypericum caused significant inhibition of intestinal P-gp, whereas long-term treatment with the herb reversed the changes in fexofenadine disposition.

7.8 Imatinib

Imatinib (STI 571, CTI 571) is a potent inhibitor of the Bcr-Abl and c-kit tyrosine kinases and is approved by the US FDA for the treatment of Philadelphia chromosome-positive chronic myeloid leukaemia and gastrointestinal stromal tumours.[239-241] Two clinical studies have been conducted to investigate the effect of hypericum treatment on the pharmacokinetics of imatinib.[242,243] In an open-label, crossover, fixed-sequence study in ten healthy volunteers, 2 weeks of treatment with hypericum at 900 mg/day significantly decreased the AUC of imatinib by 32%, C_{max} by 29% and $t_{1/2}\beta$ by 21%.[243] The protein binding of imatinib was not altered by hypericum.[243] Similar results were observed in another clinical study involving 12 healthy volunteers.[242] These results indicate that patients taking imatinib should avoid hypericum administration; however, if concomitant use of hypericum with imatinib is chosen, an increase in the imatinib dose becomes necessary to maintain clinical effectiveness.

Treatment with rifampicin (a potent CYP3A4 inducer) at 600mg once daily for 11 days significantly decreased the single dose C_{max} and AUC of imatinib by 54% and 74%, respectively.[244] Rifampicin appears to be a more potent inducer of CYP3A4 than hypericum. The magnitude of the effect of hypericum on imatinib was generally similar to that reported for hypericum on other CYP3A4 substrates such as ciclosporin and tacrolimus. In patients receiving rifampicin or other CYP3A4 inducers, alternative therapeutic agents with less CYP3A induction potential should be selected when imatinib is administered.

7.9 Irinotecan

In an unblinded, randomised crossover study involving five cancer patients it was found that treatment with hypericum 900 mg/day orally for 18 days decreased the plasma concentrations of the active metabolite of irinotecan, SN-38 by 42%.[245] This was accompanied by a decreased myelosuppression. These findings indicate that patients receiving irinotecan treatment should refrain from taking hypericum.

7.10 Methadone

Long-term treatment with hypericum 900 mg/day for a median period of 31 days (14–47 days) lowered the trough concentration of methadone by 47% in four patients.[246] Two patients reported symptoms that suggested a withdrawal syndrome. The interaction may be due to induction of CYP isoenzymes (CYP3A4, CYP2C8 and CYP2D6) that metabolise methadone.[247,248] Thus, combination of hypericum with methadone might induce withdrawal symptoms, which may lead to resumption of illicit drug use.

7.11 Oral Contraceptives

Oral hormonal contraceptives for women are divided into two types: combined (estrogen plus progestogen) and progestogen-only.[249] Oral contraceptives are one of the most highly effective forms of contraception and provide many short- and long-term noncontraceptive health benefits.[250] Most oral

contraceptives are substrates of CYP3A4 and CYP inducers.[251] Ethinyloestradiol is a major component of the contraceptive pill and is also used in hormone replacement therapy in postmenopausal women. It is metabolised through hydroxylation at the 2-position by CYP3A4.[252] Hypericum is a potent inducer of CYP3A4,[189,198,199] which raises the possibility of interactions with oral contraceptives,[253] particularly when the drug content is lowered to avoid the undesirable estrogenic effects.[254]

Breakthrough bleeding has been reported in women on the oral contraceptive pill when concomitantly taking hypericum.[255] This has also been attributed to increased CYP3A4-mediated metabolism of the steroids due to enzyme induction. It has already been observed that the contraceptive pill may fail to afford the expected protection in female patients with tuberculosis, as rifampicin (as a known CYP3A4-inducer) elevated the elimination of contraceptives.[256]

Several case reports of unexpected pregnancies and intermenstrual bleeding have been reported, mainly in young women on oral contraceptives, after taking hypericum for as little as 1 week.[257,258] Discontinuation of hypericum led to recovery in those cases in whom the outcome was known. These interactions are believed to be due to lowered drug concentrations, resulting from induction of CYP3A4, although no blood concentrations have been measured and recorded in these case reports. A recent preliminary study found that administration of hypericum extract Ze 117 did not alter blood estrogen concentrations.[259] Based on the reported interactions, women using oral contraceptives should be warned against using hypericum.

7.12 Protease Inhibitors

Some protease inhibitors have been found to interact with hypericum. Intake of hypericum (900 mg/day, standardised to 0.3% hypericin) for 2 weeks led to a decrease in the plasma AUC of indinavir by a mean of 57% and extrapolated indinavir C_{8h} by 81% in healthy volunteers (n = 8; 6 male and 2 female).[260] One spontaneous case has been reported in the UK, in which the patient experienced an increase in HIV RNA viral load following the use of hypericum concomitantly with indinavir and lamivudine. Indinavir is a CYP3A4 substrate.[261]

Reduced indinavir exposure could result in the development of drug resistance and treatment failure in patients infected with HIV. Since many other protease inhibitors, such as amprenavir[262] and saquinavir,[46] are also metabolised by the CYP3A4, they may be adversely influenced by concomitant intake of hypericum. HIV patients being treated with protease inhibitors should avoid hypericum. The European Medicine Evaluation Agency has recommended that patients receiving protease inhibitors such as indinavir for the treatment of HIV infection should not concomitantly take hypericum and other products containing this herb. Moreover, the ingestion of hypericum elevated the oral clearance of the HIV reverse transcriptase inhibitor nevirapine.[263] Nevirapine metabolism is catalysed by CYP3A4 and CYP2B6.[264]

7.13 Quazepam

A randomised, placebo-controlled, cross-over study of 13 healthy volunteers revealed that treatment with hypericum 900 mg/day significantly decreased the C_{max} and AUC of quazepam.[265] This was accompanied with an increased urinary ratio of 6β-hydroxycortisol to cortisol (a marker for CYP3A4 activity). However, hypericum did not affect the CNS effect of quazepam. These results suggest that hypericum decreases plasma concentrations of quazepam, probably through CYP3A4 induction. Quazepam is a known substrate for CYP3A4.

7.14 Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) act by inhibition of the neuronal uptake pump for serotonin, a property shared with the tricyclic antidepressants, without affecting the other various neuroreceptors or fast sodium channels.[266] Cases have been reported where the combination of hypericum and SSRIs (e.g. sertraline and nefazodone) caused symptoms characteristic of central serotoner-

gic syndrome,[267-271] particularly in the elderly. This syndrome is characterised by confusion, agitation, hyper-reflexia, shivering or tremor, diaphoresis, nausea, diarrhoea, lack of coordination, fever, coma, flushing or rhabdomyolysis.[272]

Hyperforin and other components from hypericum inhibited rat vesicular uptake of monamines including serotonin, dopamine and norepinephrine,[273,274] and long-term treatment with hypericum and hypericin increased monoamine levels in rat hypothalamus and hippocampus.[275] Unlike standard reuptake inhibitors, hypericum exerts this reuptake inhibition noncompetitively by enhancing intracellular sodium ion concentrations.[276] At a receptor level, long-term treatment with hypericum downregulates β_1-adrenoceptor and upregulates post-synaptic serotonin 5-HT_{1A} and 5-HT_2 receptors.[276] Cases of serotonin syndrome in patients taking hypericum have been reported.[277,278] Thus, an additive effect will be observed when hypericum and conventional antidepressants are combined, resulting in excessive serotonin. Since the safety profile of combining SSRIs with hypericum is not fully defined, the combined used of these two types of agents should be avoided.

7.15 Simvastatin and Pravastatin

The effects of hypericum on the pharmacokinetics of HMG-CoA reductase inhibitors simvastatin and pravastatin have been investigated in a double-blind, crossover study in 16 healthy male volunteers.[279] Hypericum caplet (900 mg/day) for 14 days decreased the C_{max} and AUC of simvastatin hydroxy acid, but not pravastatin. The interaction can be partly attributable to enhanced CYP3A4-mediated first-pass metabolism of simvastatin in the small intestine and liver by hypericum.

7.16 Tacrolimus and Mycophenolate Mofetil

A recent case report associated hypericum treatment with decreased tacrolimus concentrations in a renal transplant patient.[280] More recently, the effect of hypericum extract on the pharmacokinetics of the tacrolimus and mycophenolate mofetil in ten stable renal transplant patients was reported.[281] Treatment with hypericum extract 600 mg/day for 14 days reduced the AUC of tacrolimus by 57.8%, but the pharmacokinetics of mycophenolate mofetil remained unchanged. Dosage adjustments from a median 4.5 mg/day at baseline to 8.0 mg/day during hypericum treatment were required to maintain therapeutic tacrolimus concentrations. These findings indicated that administration of hypericum extract to patients receiving tacrolimus treatment might significantly decrease tacrolimus blood concentrations, leading to the risk of organ rejection.

7.17 Theophylline

A case was reported where a female patient required high doses of theophylline to attain therapeutic plasma concentrations.[282] The use of a high dose of this drug became necessary when the patient started taking hypericum 300 mg/day. When the ingestion of the herb was discontinued, theophylline plasma concentrations doubled, requiring dose reduction. These observations suggest that the intake of hypericum enhances the metabolism of theophylline. Theophylline is primarily metabolised by CYP1A2,[283] implying that hypericum induces the expression of this enzyme in the liver.

7.18 Warfarin and Phenprocoumon

The interaction between hypericum and warfarin had been identified from spontaneous case reports.[255,257] Seven cases of decreased warfarin effect following hypericum treatment were reported to the Swedish Medical Products Agency.[257] Between 1998 and 2000, 22 spontaneous case reports of interactions with warfarin had been reported to regulatory authorities in Europe. These interactions all resulted in unstable INR values, with a decrease in the INR value being the most commonly observed effect of hypericum.[255,257] Concomitant intake of hypericum was associated with loss of anticoagulant activity in patients stabilised on warfarin. Although no thromboembolic episodes occurred, the decrease in anticoagulant activity was considered clinically significant. Anticoagulant activity was restored when hypericum was terminated or the warfarin dose was increased.

In a crossover study, healthy volunteers taking hypericum extract LI 160 at a 900mg daily dose for 11 days before a single dose of phenprocoumon (an anticoagulant) had a lower AUC of the free fraction than when they received placebo.[284]

These observations suggest increased clearance of both warfarin and phenprocoumon, possibly because of the induction of CYPs, particular CYP2C9 and CYP3A4. Both warfarin and phenprocoumon are substrates of CYP2C9.[285] Warfarin is also metabolised by CYP1A2 and CYP3A4.[286] Intake of hypericum may induce CYP2C9 and CYP3A4, contributing to the loss of anticoagulant activity.

7.19 Mechanism Considerations

In vitro studies have demonstrated that hypericum extract was a potent inducer of CYP2B6 and CYP3A4, and the responsible constituent was hyperforin.[189,287,288] *In vitro* studies have shown that hyperforin was a potent ligand (inhibition constant [K_i] = 27 nmol/L) for the pregnane X receptor,[189] which is an orphan nuclear receptor regulating expression of CYP2B6 and CYP3A4.[227,287,288] Hypericum extracts have also been reported to inhibit the activities of recombinant CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.[187] Animal studies also indicate that hypericum is a potent modulator of various CYP enzymes using probe drugs. Administration of hypericum extract 140 or 280 mg/kg/day to mice for 3 weeks resulted in a 2-fold increase in both the CYP3A and CYP2E1 activities,[289] and the administration of hypericum extract to rats resulted in a significant increase in hepatic CYP3A4 protein expression.[227] In addition, hypericum is an inducer of CYP3A4 as indicated by increased urinary 6β-hydroxycortisol/cortisol ratio[290] and midazolam clearance in healthy volunteers.[199] Clinical studies using a probe drug cocktail indicated that long-term (2 weeks) hypericum administration significantly induced intestinal and hepatic CYP3A4, but did not alter the CYP2C9, CYP1A2 or CYP2D6 activities when probe substrates were used.[198,290] Short-term administration (3 days) had no effect on CYP3A4 activity.[198] However, there is one report that hypericum did not change the activity of CYP3A4 and CYP2D6 in healthy volunteers, but this may be due to the short duration of administration (<7 days) and the lower dose used.[197]

The magnitude of the drug interactions (e.g. digoxin) with hypericum observed in clinical reports is greater than that predicted by *in vitro* data, suggesting that induction of CYP3A4 is unlikely to explain some interactions completely and a second interaction mechanism should exist. Several studies indicate that hypericum induces intestinal P-gp *in vitro* and *in vivo*.[227,291,292] Treatment of LS-180 intestinal carcinoma cells with hypericum or hypericin at 3–300 μmol/L caused a 4- to 7-fold increase in the expression of P-gp.[292] Cells treated with hypericum long-term had decreased accumulation of rhodamine 123. The administration of hypericum extract to rats for 14 days resulted in a 3.8-fold increase of intestinal P-gp expression.[227] Oral administration of hypericum for 14 days in healthy volunteers resulted in a 1.4-fold increase in P-gp expression.[227] The probe substrates of P-gp, fexofenadine and ciclosporin were found to have increased clearance in healthy subjects treated with hypericum.[199,293] Moreover, long-term treatment with hypericum (16 days) produced a 4.2-fold increase in expression of P-gp in the peripheral blood lymphocytes of healthy volunteers.[291] This was associated with enhanced drug efflux function, resulting in reduced intracellular accumulation of rhodamine.

The induction of hepatic and intestinal CYP3A4 by hypericum may partly explain that hypericum increases the clearance of many coadministered drugs such as indinavir,[198,227,260] ciclosporin[220,288,294] and oral contraceptives,[3] as all of these drugs are substrates of CYP3A4. Because CYP3A4 is involved in the oxidative metabolism of >50% of all therapeutic drugs, hypericum is likely to interact with many more drugs than previously had been realised. Therefore, future development of hypericum derivatives lacking activating property for pregnane X receptor may enable its antidepressant activity and pharmacokinetic herb-drug interaction to be dissociated. The induction of intestinal P-

gp[227] may also partly contribute to the effects of hypericum on the pharmacokinetics of ciclosporin, indinavir and digoxin (all are substrates of P-gp).[198] Thus, hypericum has contrary modulating effects on intestinal P-gp and CYP3A compared with grapejuice. Grapefruit juice augmented the oral bioavailability of most dihydropyridines, terfenadine, saquinavir, ciclosporin, midazolam, triazolam and verapamil,[295,296] which was thought to be due to the inhibition of intestinal CYP3A4 and P-gp.[297,298]

8. *Panax ginseng* (Ginseng)

Panax ginseng (ginseng) is a widely used herbal medicine because of its purported anti-hypertensive, anti-fatigue, neuroprotective, antioxidative, chemopreventive, hypolipidaemic, cognition-enhancing, immuno-enhancing, ulcer-healing and anticancer effects.[299-303] Its major constituents include ginsenosides (panoxosides), sterols, flavonoids, peptides, vitamins, polyacetylenes, minerals, β-elemine and choline.[301,304] Ginsenosides are considered the major pharmacologically active constituents, and approximately 12 types of ginsenosides have been isolated and structurally identified. Ginsenoside Rh2, found only in red ginseng, exhibited potent cytotoxicities against several cancer cell lines.[305] Ginsenoside Rg3 was metabolised to ginsenoside Rh2 and protopanaxadiol by human fecal microflora.[306] Ginsenoside Rg3 and the resulting metabolites exhibited potent cytotoxicity against tumour cell lines.[306] Although ginseng is always considered to be well tolerated, some adverse events such as headache, sleep and gastrointestinal disorders have been reported.[307]

8.1 Alcohol (Ethanol)

An open-label, nonrandomised clinical study in healthy volunteers (n = 14) indicated that ginseng extract increased blood alcohol (ethanol) clearance by 30%.[308] This could be due to delayed gastric emptying by ginsenosides, and induction of alcohol-oxidising systems and CYP2E1. Alcohol is mainly eliminated by oxidation to acetaldehyde and acetate, catalysed predominantly by alcohol dehydrogenase (ADH I and ADH V) and aldehyde dehydrogenase.[309,310] Other alcohol oxidation pathways include catalase and microsomal alcohol-oxidising systems such as CYP2E1.[309] The monoxidative pathway generating fatty acid ethyl esters appear to play a minor role. A high dose of alcohol decreased ADH activity and the conversion of lactate to pyruvate in the liver.[310]

Ginseng treatment also appeared to accelerate the elimination of alcohol in mice[311] and rats.[312,313] Oral treatment of aqueous ginseng extract 200 mg/kg to rats decreased the AUC of alcohol by 21% when alcohol was orally administered, but no pharmacokinetic alteration was observed when alcohol was administered intraperitoneally.[313] Ginseng and ginsenosides were found to enhance exercise endurance and reduce the plasma concentration of alcohol in mice.[311] Gastric emptying was slowed by ginseng, ginsenosides or alcohol administration. An additive effect was observed when the mice were pretreated with ginseng or ginsenosides 10 minutes before alcohol administration.[311] These results suggest that ginseng decreases the plasma alcohol concentration mainly by delaying gastric emptying.

8.2 Phenelzine

Several case reports have documented suspected interactions of ginseng with the monoamine oxidase inhibitor phenelzine.[314,315] The patients presented with headache, tremulousness and manic episodes. One of these patients experienced sleeplessness, tremors and headaches and greater depression again when she reused ginseng with phenelzine (45 mg/day).[316] The mechanism underlying these interactions is unclear, but may be related to the psychoactive central effects of ginseng. Ginseng saponins and extracts have been shown to: block the nicotinic acetylcholine receptors;[317] potentiate the relaxation induced by transmural electrical stimulation or nicotine in monkey cerebral arterial strips;[318] inhibit voltage-dependent brain sodium ion channels;[319] and inhibit NMDA receptor-mediated signals in rat hippocampal neurons.[320] In addition, phenelzine undergoes extensive oxidative metabolism, resulting in phenylacetic acid and *p*-hydroxyphenylacetic

acid.[321] It is unknown whether ginseng modulates the metabolism of phenelzine.

8.3 Warfarin

Ginseng has the potential to cause drug interaction with warfarin. A 47-year-old man with a St Jude-type mechanical heart valve in the aortic position had been stabilised while receiving warfarin for 5 years, but became destabilised following administration of ginseng and several other drugs.[322] The patient's INR decreased to 1.5 after 2 weeks of concomitant ginseng, which had been preceded by an INR of 3.1. When ginseng was discontinued, the INR returned to 3.3 within 2 weeks. Thus, concomitant use of ginseng with warfarin should be avoided.

A recent study has evaluated the effect of ginseng treatment on warfarin pharmacokinetics and response.[323] Ginseng treatment did not significantly change the clearance, volumes of distribution and plasma protein binding of (*R*)- and (*S*)-warfarin. Pretreatment with ginseng also did not affect the pharmacodynamics of either (*R*)- or (*S*)-warfarin. However, treatment with American ginseng (*P. quinquefolium*) at 1.0 g/day for 3 weeks significantly reduced the INR, C_{max} and AUC of warfarin in healthy volunteers.[324]

Both pharmacokinetic and pharmacodynamic components may play a role in ginseng-warfarin interactions. Ginseng extracts have been shown to have antiplatelet effect.[325-328] Ginsenosides Rg3 and protopanaxadiol-type saponins were found to be platelet-activating factor antagonists with IC_{50} values of 49–92 μmol/L.[327] Modulation of various CYP isoenzymes is also strongly implicated as the mechanism of ginseng-warfarin interactions. A study in rats indicated that the pharmacokinetics and pharmacodynamics of warfarin after a single dose and at steady state were not altered by coadministered ginseng.[329] However, extensive *in vitro* and *in vivo* animal studies have indicated that ginseng constituents can modulate various CYP isoenzymes that metabolise warfarin.[330-334] Ginsenoside Rd caused weak inhibitory activity against recombinant CYP3A4, CYP2D6, CYP2C19 and CYP2C9, whereas ginsenoside Re and ginsenoside Rf (200 μmol/L) increased the activity of CYP2C9 and CYP3A4.[332] In the rat, the standardised saponin of red ginseng showed inhibitory effects on *p*-nitrophenol hydroxylase (CYP2E1) activity in a dose-dependent manner.[334] Obviously, further studies are warranted to explore the effects of ginseng constituents on CYP isoenzymes in humans.

8.4 Vaccines

In a multicentre, randomised, placebo-controlled, double-blind clinical study, a total of 227 volunteers who visited three private practices received daily placebo or 100mg of standardised ginseng extract for 12 weeks during which time they also received an anti-influenza polyvalent vaccination at week 4.[335] Ginseng significantly reduced the frequency of influenza or common cold, and natural killer cell activity levels at weeks 8 and 12 were nearly twice as high in the ginseng group than in the placebo group.[335] In all of the volunteers, laboratory values of 24 safety parameters showed no significant differences between the end and the beginning of the 12-week study in either of the groups.

Animal studies also provide evidence that ginseng extract acts as an immune adjuvant.[336-338] Immunisations using porcine parvovirus-vaccines adjuvanted with single purified ginsenosides demonstrated that the ginseng fractions Rb1 and Rg1 are potent adjuvants inducing higher or similar antibody titres than the vaccine adjuvanted with aluminium hydroxide.[336] Both ginseng extract and Rb1 were well tolerated adjuvants, and Rb1 had the strongest adjuvant effect, when used for immunisation against *Staphylococcus aureus* in dairy cattle.[337] Thus, the use of ginseng as a coadjuvant provides a simple, well tolerated and inexpensive alternative for improving the potency of aluminium hydroxide adjuvanted vaccines.[338] Field trials are warranted to evaluate the ability of ginseng components to enhance the efficacy of various vaccines in protection against infections.

9. *Piper methysticum* (Kava)

Piper methysticum (kava, kavain, indigenous to Polynesia, Melanesia and Micronesia) is an effec-

tive herbal medicine for the therapy of anxiety and insomnia.[339-342] Clinical studies have shown that kava and kavalactones are effective in the treatment of anxiety at subclinical and clinical levels, anxiety associated with menopause and various other medical conditions[340,341,343-345] The major constituents of kava are pharmacologically active kavalactones, which are responsible for about 95% of the total activity of kava.[339] Yangonin, desmethoxyyangonin, methysticin, 7,8-dihydromethysticin, kawain and 7,8-dihydrokawain are the kavalactones present in the highest levels, accounting for approximately 96% of lipidic extracts.[346] Several kavalactones are potent inhibitors of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP4A9 and CYP4A11.[347] This indicates that kava has a high potential for causing pharmacokinetic drug interactions.[348] In addition, several pharmacodynamic interactions have been postulated and observed.[348]

9.1 Alcohol

A clinical study indicated that kava did not alter the safety-related performances in volunteers taking alcohol.[349] However, coadministration of alcohol and kava had been shown to have additive hypnotic effects in the mouse.[350] Further study is needed to explore the safety of kava-alcohol combination.

9.2 Alprazolam

There was one case report of interaction between kava and alprazolam that may have caused a semicomatose state in a 54-year-old man.[351] The patient was taking cimetidine, alprazolam and terazosin with self-medicated kava for 3 days prior to hospitalisation. The investigators suggested that both kavalactones and alprazolam had additive effects, since both act on the same GABA receptors.[352,353] However, as alprazolam is a substrate of CYP3A4[354] and kavalactones are potent inhibitors of CYP3A4,[347] decreased elimination of alprazolam by kava may contribute to the additive effects reported upon coadministration of kava and alprazolam.

9.3 Bromazepam

A double-blind, randomised, crossover study involving 18 healthy volunteers investigated the effects of combining a kava extract 800 mg/day and bromazepam 9 mg/day for 2 weeks.[355] The results indicate that there were no significant differences between bromazepam alone and the combination therapy. Performance did not differ from baseline with kava alone. Seventy-seven adverse events were recorded, of which 22% were related to kava, 36% to bromazepam and 42% to the combination therapy. The most common adverse event was tiredness, occurring in four participants while taking kava, 11 taking bromazepam and 14 taking the combination.[355]

9.4 Levodopa

A patient with Parkinson's disease concomitantly taking levodopa and kava had increased duration and number of 'off' periods.[356] This may be explained by the dopamine antagonistic activity of kava.[357] A 45-year-old woman taking kava developed severe parkinsonism.[358] The patient, who had a family history of essential tremor, developed severe and persistent parkinsonism after days of treatment with kava extract for anxiety. The symptoms improved with acetylcholine receptor antagonists.

10. *Piper nigrum Linn* and *P. longum Linn* (Black and Long Pepper)

Both black (*Piper nigrum Linn*) and long (*P. longum Linn*) peppers have been used in spices and herbal medicines included in traditional antidiarrhoeal formulations. Piperine, a pungent alkaloid, is the major constituent present in *P. nigrum*. Piperine inhibited gastric emptying of solids/liquids in rats and gastrointestinal transit in mice in a dose- and time-dependent manner.[359] Animal studies have indicated that piperine enhanced the bioavailability of amoxicillin, cefotaxime,[360] nimesulide,[361] pentobarbital[362] and curcumin.[363] A study in healthy volunteers showed that coadministration of piperine 5 mg/day for 21 days increased the AUC of coenzyme Q10 (120mg) by approximately 30%.[364]

Thus, piperine may act as a bioavailability enhancer of drugs and other substances in humans.

10.1 Propranolol

In a crossover study involving six healthy volunteers, treatment of piperine 20mg daily for 7 days followed by a single dose of propranolol (40mg) resulted in reduced time to maximal concentration, and increased C_{max} and AUC.[365] Propranolol is mainly metabolised by CYP1A1, CYP1A2 and CYP2D6.[366-368] Inhibition of these two enzymes by piperine will increase the AUC of propranolol. In hepatoma cells expressing constitutive and inducible CYP1A, piperine caused an initial inhibition of CYP1A followed by induction phase.[369] Marked inhibition of arylhydrocarbon hydroxylase and 7-ethoxycourmarin deethylase was observed with piperine in a concentration-dependent manner in rat and guinea pig liver microsomes.[370] However, multiple doses of piperine by intraperitoneal injection (500 mg/kg/day for 3 days) to the rat resulted in an approximate 2-fold increase in total liver microsomal CYP content, 7-ethoxycoumarin deethylase (CYP1A) and the hepatic hexobarbital hydroxylase (CYP2B1) activity, and CYP2B1/2 and CYP1A protein levels.[371] The enhanced systemic availability of oral propranolol could be exploited to achieve better therapeutic control and improved patient compliance.

10.2 Rifampicin (Rifampin)

Administration of piperine significantly increased plasma rifampicin concentrations in patients with pulmonary tuberculosis.[372] Rifampicin is a substrate of P-gp.[373] The inhibition of P-gp by piperine is the possible mechanism for the interaction. Piperine inhibited digoxin and ciclosporin (both typical P-gp substrates) transport in Caco-2 cells with IC_{50} values of 15.5 and 74.1 μmol/L, respectively.[374]

10.3 Spartein

P. longum increases the blood concentration of spartein by 100% in healthy volunteers.[375] The observed interaction may be ascribed to increased absorption of sparteine (a CYP2D6 substrate) from the gastrointestinal tract and decreased drug metabolism in their first passage through the liver after being absorbed. An intragastric dose of piperine 100 mg/kg to rats caused an increase in total CYP content.[370,376]

10.4 Theophylline

Treatment of piperine 20mg daily for 7 days followed by a single dose of theophylline 150mg in healthy volunteers resulted in increased C_{max} and AUC, and decreased $t_{1/2}\beta$.[365] Theophylline is mainly metabolised by CYP1A1 and CYP1A2, while CYP2E1 and CYP2D6 only play a minor role.[377,378] The altered pharmacokinetics of theophylline by piperine are considered to be due to inhibition of these CYP isoforms.

10.5 Phenytoin

In mice, rats and humans coadministration of oral piperine significantly increased the absorption constant and AUC, and delayed elimination of phenytoin.[379,380] Intravenous phenytoin in the oral piperine-treated rat group showed a significant alteration in the elimination phase, indicating its metabolic impairment.[379] It was shown that a single dose of kava 1g more than doubled the AUC and $t_{1/2}\beta$ of phenytoin.[379] The interaction may be due to the inhibition of both P-gp and CYP2C9 and 3A. Piperine inhibited recombinant CYP3A4 activity[381] and CYP3A4-mediated verapamil oxidation in human liver microsomes.[374] Phenytoin is hydroxylated by CYP2C9, CYP2C19, CYP3A4, CYP3A5 and CYP3A7 to its primary phenol metabolite, 4'-hydroxyphenyl-5-phenylhydantoin.[382-386] 4'-Hydroxyphenyl-5-phenylhydantoin was further oxidised by CYP2C9, CYP2C19 and CYP3A to 3',4'-dihydroxyphenyl-5-phenylhydantoin.[386] Phenytoin is also a substrate of P-gp.[387] Since piperine inhibits both P-gp and CYP3A4 expressed in enterocytes and hepatocytes and contributes to a major extent to first-pass elimination of many drugs,[388] piperine may alter the plasma concentrations of drugs that are P-gp and CYP3A4 substrates, particularly when these drugs are administered orally.

11. *Salvia miltiorrhiza* (Danshen)

The root of *Salvia miltiorrhiza* is known as danshen in traditional Chinese medicine. It is mainly used for the treatment of cardiovascular diseases, including angina pectoris, myocardial infarction and stroke.[389] The major active constituents of *S. miltiorrhiza* root are tanshinones,[390] which have been reported to have antiplatelet,[391,392] cardioprotective,[393-395] anti-inflammatory,[396] hepatoprotective,[397,398] nephroprotective,[399] antimutagenic[400] and anti-HIV[401] effects in preclinical studies. It also has immunomodulating,[402,403] antioxidant and radical-scavenging,[404,405] antihypertensive,[406] ulcer-healing,[407] antiangiogenic[408] and anticancer activity.[409,410]

11.1 Warfarin

Three cases have been published reporting enhanced anticoagulation and bleeding when patients on long-term warfarin therapy consumed *S. miltiorrhiza* root.[411] As these patients were also taking other medications, the contribution of *S. miltiorrhiza* root to the interaction was difficult to determine. However, for safety reasons, the combination of *S. miltiorrhiza* root and warfarin should be avoided. The anticoagulant activity of *S. miltiorrhiza* root itself may provide a partial explanation for the interactions.[411]

However, pharmacokinetic interactions may also play a role. A rat study has found that treatment with *S. miltiorrhiza* root extract 5 g/kg twice daily for 3 days followed by a single oral dose of racemic warfarin increased the absorption rate constants, AUC, C_{max} and $t_{½}\beta$ of warfarin, but decreased the clearance and apparent volume of distribution of both (*R*)- and (*S*)-warfarin.[412,413] A similar effect was observed at steady-state levels of warfarin. The anticoagulant effect of warfarin was also potentiated. Interestingly, *S. miltiorrhiza* root extract itself had no effect on prothrombin time at this dose level in the rat,[413] suggesting that altered warfarin metabolism was a possible mechanism for the interactions observed. Warfarin is mainly metabolised by CYP2C9 and to a lesser extent by CYP1A2 and CYP3A4.[286]

In addition, *S. miltiorrhiza* root extract may change the plasma protein binding of warfarin. It is well known that both (*R*)- and (*S*)-warfarin bind to the so-called site I of albumin with high affinity.[414,415] *S. miltiorrhiza* root extract was bound by albumin up to 70%.[416] *In vitro S. miltiorrhiza* root extract displaced salicylate from protein binding, thereby increasing the free salicylate concentration.[416] However, Kangen-Karyu, a mixture of six herbs, significantly increased the plasma warfarin concentration and prothrombin time in the rat,[417] but it did not influence the serum protein binding of warfarin. Further studies are required to explore the effects of *S. miltiorrhiza* root extract on the metabolism and plasma protein binding of drugs such as warfarin in humans.

12. *Scutellaria baicalensis* (Huangqin)

Huangqin, the root of *Scutellaria baicalensis*, is a traditional Chinese herb medicine used as an anti-inflammatory agent and smooth muscle relaxant against bacterial infections of the respiratory and the gastrointestinal tracts.[418] The major active components of *S. baicalensis* root are flavonoids, including baicalin (12–17%) and its aglycone baicalein, wogonoside and its aglycone wogonin.[419] Baicalin and baicalein have been reported to have anti-allergic,[420] anti-inflammatory,[421,422] antioxidant and free radical-scavenging,[423,424] and anticancer activity.[425] Pharmacokinetic studies indicated that baicalin was absorbed as baicalein after hydrolysis in the gastrointestinal tract,[426] with a bioavailability of 64% in rats.[427] Baicalin and wogonin are mainly excreted in the urine as glucuronides and sulphates in the rat and humans.[428,429]

12.1 Irrinotecan

Irinotecan (CPT 11) is a potent DNA topoisomerase I inhibitor used in the treatment of advanced colorectal and lung cancer, giving an objective response in about 20% of treated patients.[430-432] As a prodrug, irinotecan is converted to its active metabolite 7-ethyl-10-hydroxy-camptothecin (SN-38) by two isoforms of human liver carboxylesterase.[433-435] SN-38 is further converted to a glucuro-

nide by uridine diphosphate glucuronosyltransferase (UGT) 1A1 and UGT1A9.[436-438] The major toxicity of irinotecan is late-onset diarrhoea,[439,440] which has been mainly attributed to the toxic effect of the active metabolite SN-38 on intestinal epithelia.[441] A recent randomised study in 44 previously untreated patients with advanced non-small-cell lung cancer revealed that oral TJ 14 (major component of *S. baicalensis* root extract) 7.5 g/day ameliorated irinotecan-induced diarrhoea severity and also reduced the frequency of diarrhoea grades 3 and 4.[442] Similarly, treatment of rats with baicalin 25 mg/kg orally twice daily or Kampo medicines (TJ 14 and TJ 114; 125mg to 1000 mg/kg orally twice daily) from the day before to 4 or 10 days after the start of irinotecan administration resulted in significantly decreased diarrhoea and histological injuries, and accelerated healing of the intestinal tract.[443,444]

The mechanism for this may be multifactorial. The study in rat indicated that TJ 14 significantly suppressed increased colonic prostaglandin E_2 by irinotecan, which is closely related to the onset of diarrhoea.[445] Baicalin is a β-glucuronidase inhibitor, and may reduce the deconjugation of SN-38 glucuronide to toxic SN-38 in the intestine.[446] TJ 14 also increased colonic water absorption impaired by repeated administration of irinotecan in rats.[445] In addition, baicalein, the major component in TJ 14, may modulate P-gp function and thus alter the disposition of irinotecan and SN-38. Evidence has indicated that the biliary excretion of both irinotecan and SN-38 depends on the presence of drug-transporting proteins, notably P-gp and canalicular multispecific organic anion transporter, which are present on the bile canalicular membrane.[439,447-449]

13. *Silybum marianum* (Milk Thistle)

Silybum marianum (milk thistle) is one of the most commonly used herbal medicines. It is reported to contain a number of flavonolignans,[450-452] which are generated in plants by radical coupling of a flavonoid and a phenylpropanoid. Silymarin, a mixture of these flavonolignans isolated from an extract of *S. marianum* fruit, is composed of mainly silibinin (silybin) [50–80%], with small amounts of other flavonolignans such as silychristin or silydianin.[453-455] A standardised extract of *S. marianum* contains at least 70% silymarin. Silibinin is primarily conjugated (both glucuronidation and sulfation) and excreted in the bile and urine in rats[456] and humans.[457-460] Thus, there would be competition between silymarin and other drugs and endogenous substances that are metabolised by UGTs to glucuronides in the liver. Silymarin has been reported to decrease bilirubin conjugation in patients with liver cirrhosis.[461]

13.1 Indinavir

The effect of *S. marianum* on the pharmacokinetics of indinavir has been investigated in healthy volunteers by Piscitelli et al.[462] and DiCenzo et al.[463] In the study by Piscitelli et al.,[462] treatment with *S. marianum* at 175mg (equivalent to silymarin 153mg) three times daily for 3 weeks caused a 9% and 25% reduction ($p > 0.05$) in the AUC from 0 to 8 hours (AUC_8) and mean C_{8h} of indinavir. Similar results were observed in the study by DiCenzo et al.[463] It appears the interaction was insignificant and should not interfere with indinavir therapy in AIDS patients. The minor reduction in the AUC of indinavir may be due to minor to moderate modulation of CYP3A or P-gp. Silibinin had little effect on the metabolism of erythromycin (CYP3A4), chlorzoxazone (CYP2E1), *S*(+)-mephenytoin (CYP2C19), caffeine (CYP1A2) or coumarin (CYP2A6) in human liver microsomes.[464] However, incubation of human hepatocytes with a high concentration of silymarin (0.1 or 0.25 mmol/L) significantly decreased CYP3A4-mediated 6-β-hydroxylation of testosterone.[465] Notably, silibinin has been found to be a mechanism-based inhibitor for CYP3A4 and CYP2C9.[466] These studies indicated that metabolic interactions with drugs that are mainly metabolised by CYP2E1, CYP2D6, CYP2C9 and CYP3A4 cannot be totally ruled out, since its biliary concentrations may be up to 200 μmol/L.[459,460,467]

In a recent clinical study, treatment with *S. marianum* for 28 days did not significantly affect CYP1A2, CYP2D6, CYP2E1 or CYP3A4 activi-

ty,[468] when probe drug cocktails of midazolam and caffeine were used, followed 24 hours later by chlorzoxazone and debrisoquine. Similarly, treatment with *Citrus aurantium*, *Echinacea purpurea* or *Serenoa repens* (saw palmetto) extracts for 28 days did not affect any of these CYP isoenzymes.[468] It appears that all of these herbs, including *S. marianum*, have limited clinical impact on drugs that are mainly metabolised by CYP1A2, CYP2D6, CYP2E1 and CYP3A4.

Modulation of P-gp by *S. marianum* may cause drug interactions and alter the response to anticancer drugs that are P-gp substrates. *In vitro* studies indicated that silymarin significantly modulated P-gp. It increased daunorubicin accumulation in P-gp-positive cells, but not P-gp-negative cells, in a drug concentration- and P-gp expression level-dependent manner.[469] Silymarin potentiated doxorubicin cytotoxicity in P-gp-positive cells, while it inhibited P-gp adenosine triphosphatase activity and azidopine photoaffinity labeling of P-gp, suggesting a direct interaction with P-gp substrate binding.[469] Silibinin potentiated doxorubicin-induced growth inhibition and apoptosis,[470] and showed high affinity for direct binding to P-gp *in vitro*.[471] These findings indicated that silymarin and its metabolite inhibited P-gp-mediated cellular efflux, raising a potential for significant drug interactions with P-gp substrates.

13.2 Ursodeoxycholic Acid

Ursodeoxycholic acid is a well tolerated and effective drug for most patients with primary biliary cirrhosis, but some patients show an incomplete response.[472] Its beneficial effect is considered to be mainly due to protection of cholangiocytes against cytotoxicity of hydrophobic bile acids, stimulation of hepatobiliary secretion and protection of hepatocytes against bile acid-induced apoptosis.[473] As silymarin is a potent antioxidant with immunomodulatory and antifibrotic properties, its safety and efficacy had been evaluated in patients with primary biliary cirrhosis showing a suboptimal response to ursodeoxycholic acid (13–15 mg/kg/day for 7–221 months) therapy as indicated by persistent elevation of alkaline phosphatase activity.[474] Twenty-seven patients on ursodeoxycholic acid 13–15 mg/kg/day were simultaneously treated with oral silymarin 140mg three times daily for 1 year. No significant changes in serum alkaline phosphatase activity, total bilirubin, aspartate transaminase or Mayo risk score were noted after 1 year of treatment with combination therapy. Transitory gastrointestinal adverse events were recorded in two patients. It appears that silymarin did not provide benefit to patients with primary biliary cirrhosis responding suboptimally to ursodeoxycholic acid.

13.3 Preclinical Studies: Alcohol, Amiodarone, Cisplatin and Ciclosporin

Silibinin dihemisuccinate decreased the alcohol metabolic rate of rats.[484] This effect is ascribed to inhibition of the microsomal alcohol-oxidising system (mainly CYP2E1), which may be related to antioxidant and radical-scavenging properties of silibinin.[485] Alcohol metabolism by CYP2E1 produces free radical intermediates such as hydroxyethyl radicals.[309] However, silibinin treatment did not alter alcohol dehydrogenase, catalase and nicotinamide adenine dinucleotide phosphate hydrogen cytochrome c reductase activity.[484] It appears that a single dose of silibinin did not change the pharmacokinetics of alcohol in rats.[486]

A study in anaesthetised rats indicated that silymarin enhanced the antiarrhythmic effect of amidarone during a 10-minute reperfusion after a 5-minute coronary artery occlusion.[487] Amiodarone is a class III antiarrhythmic agent used in the treatment of symptomatic and life-threatening supraventricular and ventricular dysrhythmias such as ventricular fibrillation or haemodynamically unstable ventricular tachycardia.[488] It is mainly metabolised to an active metabolite, desethylamiodarone by CYP2C8 and CYP3A4 in humans.[489-491] It is unclear whether silymarin modulated the metabolic activation of amiodarone.

Silibinin and its derivative silipide enhanced the antitumour activity of cisplatin *in vitro*[492] and in mice.[493] Silibinin alone was unable to produce a relevant *in vitro* growth inhibition of A2780 cells,

Table I. Reported herb-drug interactions

Herb and drug	Other concomitant drugs	Study type/no. of subjects	Outcomes of interaction	Possible mechanism	Reference
***Allium sativum* (garlic)**					
Saquinavir	None	op, co/10 HV	↓ AUC by 51%, ↓ C_{8h} by 49%, ↓ C_{max} by 54%	Induction of CYP3A4 and P-gp	48
Ritonavir	None	op, co/10 HV	↓ AUC by 17%, ↔ C_{max}	Minor induction of CYP3A4 and P-gp	51
Warfarin	Not indicated	cr/2 pts	↑ INR and clotting time	Additive effect	56
Chlorpropamide	None	cr/1 pt	Hypoglycaemia	Additive effect	66
***Angelica sinensis* (danggui, Dong Quai)**					
Warfarin	Digoxin, furosemide (frusemide)	cr/1 pt	↑ INR	Herb as COX inhibitor	102
Warfarin	None	cr/1 pt	↑ INR to 10, bruising	Herb as COX inhibitor	475
***Areca catechu* (betel nut)**					
Procyclidine	Fluphenazine, flupenthixol	cr/2 pts	Severe extrapyramidal symptoms (rigidity, tremor, bradykinesis)	Antagonism of procyclidine by arecoline	476
***Eleutheroccus senticosus* (Siberian ginseng)**					
Digoxin	Paracetamol (acetaminophen), cimetidine, oxazepam, aspirin (acetylsalicylic acid), magaldrate	cr/1 pt	↑ Digoxin concentration	Interference with assay	114
***Ginkgo biloba* (ginkgo)**					
Thiazide diuretic	None	cr/1 pt	↑ Blood pressure	Metabolic inhibition	20
Trazodone	Bromazepam, donepezil, tocopherol (vitamin E)	cr/1 pt	Coma	Increase of GABAergic activity and inhibition of CYP3A4	132
Warfarin	None	cr/1 pt	PT 16.9, PTT 35.5, left parietal haemorrhage	Additive effect	477
Aspirin	None	cr/1 pt	Spontaneous hyphaema	Additive effect	140
Digoxin	None	op, co/8 HV	↑ AUC by 21.9%, ↔C_{max} and $t_{½β}$	Modulation of P-gp?	150
***Hypericum perforatum* (St John's wort)**					
Amitriptyline	None	op/12 pts	↓ AUC (amitriptyline) by 22% and nortriptyline by 41%	Induction of CYP3A and P-gp	192
Midazolam	None	op, co/12 HV	↑ Oral CL by 108.9% and ↓ oral bioavailability by 39.3%; ↓ 20% of AUC (IV)	Induction of CYP3A4	198
Midazolam	None	op, co/21 HV	↑ 1.5-fold (IV) and 2.7-fold (oral) of CL	Induction of CYP3A4	199

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Table I. Contd

Herb and drug	Other concomitant drugs	Study type/no. of subjects	Outcomes of interaction	Possible mechanism	Reference
Ciclosporin (cyclosporin)	None	cr/1 pt	↓ Blood concentration by 75%	Induction of CYP	478
Ciclosporin	None	cr/1 pt	↓ Blood concentration, rejection reaction	Induction of CYP	479
Ciclosporin	Prednisone	cr/1 pt	↓ Blood concentration	Induction of CYP	479
Ciclosporin	Unreported drugs	cs/30 pts	↓ Blood concentration by 47% (33–62%)	Induction of CYP	220
Ciclosporin	None	cs/45 pts	↓ Blood concentration by 30–64%, rejection event in 1 pt	Induction of CYP	480
Ciclosporin	None	cs/5 pts	↓ Blood concentration	Induction of CYP	481
Ciclosporin	Azathioprine, corticosteroids	cr/1 pt	↓ Blood concentration, rejection episode	Induction of CYP	216
Ciclosporin	Acetyldigoxin	cr/1 pt	Rejection episode	Induction of CYP	219
Ciclosporin	Other immunosuppressive agents	cr/1 pt	↓ Blood concentration, rejection episode	Induction of CYP	257
Ciclosporin	Mycophenolate mofetil or prednisone	cr/2 pts	↓ Blood concentration, rejection episode in 1 pt	Induction of CYP	482
Ciclosporin	None	op/11 pts	↓ AUC by 46%, C_{max} by 42%, trough concentration by 41%, altered metabolite profiles	Induction of CYP	221
Theophylline	Furosemide, potassium, morphine, zolpidem, valproic acid (valproate sodium), ibuprofen, amitriptyline, zafirlukast, triamcinolone, salbutamol (albuterol), prednisone	cr/1 pt	↓ Blood concentration	Induction of CYP	282
Imatinib	None	op, co/10 HV	↓ AUC by 32%, C_{max} by 29%	Induction of CYP	243
Imatinib	None	op, fs/12 HV	↓ AUC by 30%, ↑ CL by 42%	Induction of CYP	242
Warfarin	None	cs/7 pts	↓ INR	Induction of CYP	257
Digoxin	None	pc, pg/25 HV	↓ AUC by 25%, C_{max} by 33%, trough concentration by 26%	Induction of P-gp	224
Fexofenadine	None	op, co/12 HV	↓ C_{max} by 45% and oral CL by 20% (single dose of herb)	Inhibition of P-gp	238
Indinavir	None	op, co/8 HV	↓ AUC by 57%, extrapolated C_{8h} by 81%	Induction of CYP	260
Irinotecan	None	op, co/5 pts	↓ SN-38 by 42%	Modulation of enzyme and P-gp?	245
Methadone	None	cs/4 pts	↓ trough concentration by 47%	Induction of CYP	246
Oral contraceptives	None	cs/3 pts	Intermenstrual bleeding	Induction of CYP	479
Oral contraceptives	None	cs/9 pts	Intermenstrual bleeding	Induction of CYP	257
Loperamide	Valerian	cr/1 pt	Acute delirium episode	MAO inhibition	483

Continued next page

Table I. Contd

Herb and drug	Other concomitant drugs	Study type/no. of subjects	Outcomes of interaction	Possible mechanism	Reference
Tacrolimus	None	op, co/10 pts	↓ AUC by 57.8%	Induction of CYP	281
Simvastatin	None	co, db/16 HV	↓ C_{max} and AUC of simvastatin hydroxy acid	Induction of CYP	279
Nefazodone	None	cr/1 pt	Nausea, vomiting, headache	Additive effect on serotonin uptake inhibition	267
Sertraline	1 pt: none; 1 pt: aspirin, vitamins; 1 pt: insulin	cs/4 pts	Nausea, vomiting, anxiety, confusion, restlessness	Additive effect on serotonin uptake inhibition	267
Sertraline	Testosterone	cr/1 pt	Manic episode	Additive effect on serotonin uptake inhibition	269
Paroxetine	None	cr/1 pt	Nausea, weakness, lethargy	Additive effect on serotonin uptake inhibition	268
Panax ginseng **(ginseng)**					
Alcohol (ethanol)	None	op/14 HV	↑ Blood CL by 30%	Delayed gastric emptying and enzyme induction	308
Phenelzine	None	cr/1 pt	Headache, insomnia, tremor	Unknown	314
Phenelzine	Lorazepam, triazolam	cr/1 pt	Manic symptoms	Unknown	315
Warfarin	Diltiazem, nitroglycerin (glyceryl trinitrate), salsalate	cr/1 pt	↓ INR to 1.5	Additive effect	322
Piper methysticum **(kava)**					
Alprazolam	Cimetidine, terazosin	cr/1 pt	Coma (lethargy, disorientation)	Additive effect	351
Levodopa	Benserazide	cr/1 pt	↑ 'Off' period (number and duration)	Unknown	356
Piper nigrum Linn **(piperine)**					
Propranolol	None	op, co/6 HV	↓ time to C_{max}, ↑ C_{max} and AUC	Inhibition of CYP isoenzymes	365
Theophylline	None	op, co/6 HV	↑ C_{max}, $t_{½\beta}$, AUC	Inhibition of CYP isoenzymes	365
Salvia miltiorrhiza **(danshen)**					
Warfarin	Digoxin, propranolol, topical oil with 15% salicylates	cr/1 pt	↑ INR	Additive effect	392
Warfarin	Digoxin, furosemide, captopril	cr/1 pt	↑ INR	Additive effect	20
Warfarin	Digoxin, furosemide, theophylline, mefenamic acid	cr/1 pt	↑ INR	Additive effect	102
Silybum marianum **(milk thistle)**					
Indinavir	None	op, co/10 HV	↓ AUC by 9%, ↓ C_{8h} by 25%	Modulation of CYP3A and P-gp	462

AUC = area under the plasma concentration-time curve; **C_{8h}** = trough plasma concentration at 8 hours; **CL** = clearance; **C_{max}** = maximal plasma concentration; **co** = crossover; **COX** = cyclo-oxygenase; **cr** = case report; **cs** = case series; **CYP** = cytochrome P450; **db** = double-blind; **fs** = fixed sequence; **HV** = healthy volunteers; **INR** = international normalised ratio; **IV** = intravenous; **MAO** = monoamine oxidase; **op** = open-label; **pc** = placebo-controlled; **pg** = parallel group; **P-gp** = P-glycoprotein; **PT**= prothrombin time; **pt(s)** = patient(s); **PTT** = partial thromboplastin time; **$t_{½\beta}$** = elimination half-life; ↑ indicates increase; ↓ indicates decrease; ↔ indicates unchanged.

but silipide showed antiangiogenic effect in Matrigel assay.[493] Interestingly, pretreatment of rats with silibinin ameliorated cisplatin-induced renal toxicity.[494,495] Cisplatin is one of the most active cytotoxic agents in the treatment of testicular cancer[496] and gynaecological malignancies,[497,498] but its use is associated with ototoxicity, neurotoxicity and nephrotoxicity.[499] These results suggest that silibinin could act as a nephroprotectant and might have beneficial effects on the kidney in clinical settings, but clinical evidence is needed.

The effects of silibinin on ciclosporin-induced nephrotoxicity have been investigated.[500] Silibinin 5 mg/kg decreased ciclosporin-induced lipid peroxidation with an increased total content of hepatic CYP isoenzymes, but no protective effect on glomerular filtration rate. In addition, silibinin protected against ciclosporin-induced exocrine pancreas toxicity, as indicated by attenuated inhibition of amylase secretion.[501] Silibinin inhibited glucose-stimulated insulin release *in vitro*, without affecting blood glucose concentration *in vivo*. Silibinin may also protect the exocrine pancreas against other insults such as alcohol.

14. Conclusion

Despite the widespread use of herbal medicines, documented herb-drug interactions are sparse and many of the observed herb-drug interactions are based on individual case reports and case series (table I). Although some herb-drug interactions may be beneficial by enhancing the efficacy and reducing the toxicities of the coadministered drugs, in many cases the herb-drug interactions may increase drug toxicity or even be fatal. Thus, more studies are needed to confirm and assess the clinical significance of these potential herb-drug interactions.

The clinical importance of herb-drug interactions depends on factors that are related to coadministered drugs (dose, dosage regimen, administration route, pharmacokinetics and therapeutic range), herbs (species, dose, dosage regimen and administration route) and patients (genetic polymorphism, age, gender and pathological conditions).[502] Generally, a doubling or more in drug plasma concentration/AUC has the potential for enhanced adverse effects. However, less marked changes may still be clinically important for drugs with a steep concentration-response relationship or a narrow therapeutic index. In most cases, the extent of herb-drug interaction varies markedly among individuals, depending on interindividual differences in drug-metabolising enzymes (in particular CYP3A4) and transporters (e.g. P-gp), existing medical condition, age and other factors.[503,504] Because of the difficulties in determining the specific constituents responsible for the inhibition of CYP isoenzymes and/or P-gp, it appears to be very difficult to predict herb-drug interactions.[505]

Herb-drug interactions are much more difficult to characterise and resolve, because of the lack of comprehensive federal regulations regarding safety, efficacy and manufacturing standards for herbal medicines. It has been proposed that herbs are appropriately labeled to alert consumers to possible interactions with other concomitantly used drugs and to recommend a consultation with their general practitioner, pharmacist and/or other medical carers. It is time to consider herbs not as alternative medicine based on tradition and experience, but as phytotherapy, an integrated part of medical treatment. Regulations with regard to safety (e.g. herb-drug interactions), quality and efficacy of herbs would be highly desirable. Thus, monitoring of adverse events when herbal medicines are coadministered with drugs could be systematically carried out and potential herb-drug interactions be identified. This would enable more accurate product labelling and a body of useful information on potential herb-drug interactions to medical professionals.

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Correspondence and offprints: Dr *Shufeng Zhou*, Department of Pharmacy, Faculty of Science, National University of Singapore, Science Drive 4, Singapore 117543.
E-mail: phazsf@nus.edu.sg