Herb–drug interactions: an overview of the clinical evidence

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ABSTRACT

Herbal medicines are mixtures of more than one active ingredient. The multitude of pharmacologically active compounds obviously increases the likelihood of interactions taking place. Hence, the likelihood of herb–drug interactions is theoretically higher than drug–drug interactions, if only because synthetic drugs usually contain single chemical entities. Case reports and clinical studies have highlighted the existence of a number of clinically important interactions, although cause-and-effect relationships have not always been established. Herbs and drugs may interact either pharmacokinetically or pharmacodynamically. Through induction of cytochrome P450 enzymes and/or P-glycoprotein, some herbal products (e.g. St John's wort) have been shown to lower the plasma concentration (and/or the pharmacological effect) of a number of conventional drugs, including cyclosporine, indinavir, irinotecan, nevirapine, oral contraceptives and digoxin. The majority of such interactions involves medicines that require regular monitoring of blood levels. To date there is less evidence relating to the pharmacodynamic interaction. However, for many of the interactions discussed here, the understanding of the mechanisms involved is incomplete. Taking herbal agents may represent a potential risk to patients under conventional pharmacotherapy.

INTRODUCTION

During the last decade, an explosion in the consumption of herbal remedies has been witnessed in North America and Europe, particularly in Germany, which leads the world in the sales of such remedies, and France [1]. Surveys show, for instance, that two-thirds of women use herbs for perimenopausal symptoms, 45% of parents give their children herbal treatments and 45% of pregnant women try herbal remedies [2]. The vast majority of these products are unlicensed and are not required to demonstrate efficacy, safety, or quality [3]. Although herbs are often promoted as natural and therefore harmless, they are not free from adverse effects. A recent observational study indicates that herbal supplements are associated with adverse events that include all levels of severity, organ systems, and age groups [4].

A relevant safety concern associated to the use of herbal medicines is the risk of interaction with prescription medications [5–11]. This issue is especially important with respect to drugs with narrow therapeutic indexes, such as warfarin or digoxin [11]. Recent examinations have indicated that as many as 16% of prescription drug users consume herbal supplements [12]. Moreover, fewer than 40% of patients disclose their herbal supplement usage to health care providers and many physicians are unaware of the potential for herb–drug interactions [13]. This lack of information, combined with the fact that herbal medicines are usually mixtures of more than 100 active ingredients, obviously increases the likelihood of interactions.

The aim of this article is to highlight the clinical interactions between herbal remedies and prescribed drugs. Theoretical herb drug interactions, which are based on in vitro experiments, animal studies, speculative and/or empirical evidence can be found elsewhere [14]. *Table I* reports the herbal remedies involved in clinical herb–drug interactions.

Table I Herbal medicines involved in drug interactions. Data extracted from Capasso et al. [1] and Hennessy et al. [34].

Herbal medicine: common name/Latin name/source	Main constituent(s)	Main pharmacological action(s)	Condition(s) frequently treated
Betel nut/Areca catechu/seeds	Arecoline	Direct-acting cholinergic agonist	None (used as a relaxing/refreshing drug)
Boldo/Peumus boldus/leaves	Boldine	Choleretic/cholagogue, diuretic	Indigestion, constipation, hepatic ailments
Chinese wolfberry/Lycium barbarum/fruits	Polysaccharides, glycoproteins, vitamin C	Immunostimulant, hypoglycaemic	Loss of energy. Diabetes, liver and kidney disorders
Cranberry/Vaccinium macrocarpon/fruits	Fructose, anthocyanins, flavonoids	Antibacterial	Urinary tract infections
Curbicin[a]	Fatty acids, phytosterols, polysaccharides	Antiandrogenic, anti-inflammatory	Benign prostatic hyperplasia
Danshen/Salvia milthiorriza/roots	Tanshinones, phenolic compounds	Vasorelaxant, anti-ischaemic, antiplatelet, radical scavenger	Angina, myocardial infarction, ischaemic diseases
Dong quai/Angelica sinensis/roots	Phytoestrogens, flavonoids, coumarins	Estrogenic effects, anti-inflammatory, vasorelaxant	Gynaecological disorders, circulation conditions
Devils claw//Harpagophytum procumbens/tubers	Harpagoside	Anti-inflammatory, anti-arrhythmic, positive inotropic	Musculoskeletal and arthritic pain
Echinacea/Echinacea species/roots and aerial parts	Polysaccharides, phenols, alkamides	Immunostimulant	Infection of the upper respiratory tract
Evening primrose/Oenothera biennis/seeds	Essential fatty acids	Anti-inflammatory	Dermatological conditions, rheumatoid arthritis
Fenugreek/Trigonella foenum-graecum/seeds	Alkaloids, flavonoids, saponins	Antilipidaemic, hypoglycaemic, cholagogue	Diabetes mellitus, hypercholesterolemia,
Ginger/Zingiber officinale/rhizome	Pungent principles (gingerols, zingerone)	Antiemetic, antiplatelet, anti-inflammatory antiulcer	Prevention of nausea, dyspepsia
Ginseng/Panax ginseng/roots	Triterpene saponins (ginsenosides)	Immunomodulatory, anti-inflammatory, antitumor, hypoglycaemic	Loss of energy and memory, stress states, male sexual dysfunction
Garlic/Allium sativum/bulb	Alliins	Antihypertensive, antidiabetic, antiplatelet, antilipidaemic	Hypercholesterolemia, prevention of arteriosclerosis
Ginkgo/Ginkgo biloba/leaves	Ginkgolides, flavonoids	Increase of microcirculatory blood flow, antiplatelet, free radical scavenging	Circulatory disorders
Green tea/Camellia sinensis/leaves	Polyphenols, caffeine	Antioxidant, antilipidaemic, antitumoral, CNS stimulant	Prevention of cancer, cardiovascular diseases
Guar gum/Cyamopsis tetragonolobus/seeds	Galactomannan, lipids, saponins	Antihyperglycaemic, antilipidaemic	Diabetes, obesity, hypercholesterolemia
Kava/Piper methysticum/rhizome	Kavapyrones	Anxiolytic, anaesthetics, muscle relaxant	Anxiety, insomnia
Khat/Catha edulis/leaves	Catinone	Central stimulant and indirectly sympathomimetic	Loss of energy (khat-chewing is also as a social event)
Liquorice/Glycyrrhiza glabra roots	Glycyrrhizinic acid	Expectorant, anti-inflammatory, antiulcer, aldosterone-like effects	Gastric ulcer, catarrhs, inflammation
Papaya/Carica papaya/fruits	Papain (enzyme)	Proteolytic, lipolytic activity	Indigestion, obesity
PC-SPES[b]	Polysaccharides, phytosterols, fatty acids, flavonoids	Immunostimulant, cytotoxic	Prostate cancer
Psyllium/Plantago spp./seeds	Mucilages	Modifies gut viscosity	Constipation, overweight
Red yeast rice[c]	Monacolins	Hypocholesterolaemic	Hypercholesterolaemia
Siberian ginseng/Eleutherococcus senticosus/roots	Eleutherosides	Immunomodulatory, anti-inflammatory, antitumor,	Loss of energy and memory, stress states, male sexual dysfunction
Soya/Glycine max/beans	Phytoestrogens	Hepatoprotective, anti-osteoporosis	Treatment of menopausal symptoms, prevention of heart diseases and cancer
St John's wort/Hypericum perforatum/aerial parts	Hypericin, hyperforin, flavonoids	Antidepressant, antiretroviral	Mild to moderate depression

[a]Curbicin contains Serenoa repens (saw palmetto) fruits, Cucurbita pepo (pumpkin) seeds and vitamin E.
[b]PC-PCS is a mixture of eight herbal drugs, namely Dendrathema morofolium (chrysanthemum), Isatis indigotica (dyer's woad), Glycyrrhiza glabra (liquorice), Ganoderma lucidum (reishi), Panax pseudoginseng (san-qui ginseng), Rabdosia rubescens (rubescens), Serenoa repens (saw palmetto), Scutellaria bacicalensis (Baikal skullcap).
[c]Red yeast rice is produced by fermentation of cooked rice using the fungus Monascus purpureus.

MECHANISMS OF HERB–DRUG INTERACTIONS

Herbal medicines follow modern pharmacological principles. Hence, herb–drug interactions are based on the same pharmacokinetic and pharmacodynamic mechanisms as drug–drug interactions [15]. Pharmacokinetic interactions have been more extensively studied and in vitro and in vivo studies indicated that the altered drug concentrations by co-administered herbs may be attributable to the induction (or inhibition) of hepatic and intestinal drug-metabolizing enzymes [particularly cytochrome P450 (CYP)], and/or drug transporters such as P-glycoprotein [16,17].

The CYP is the most important phase I drug-metabolizing enzyme system, responsible for the metabolism of a variety of drugs. Many herbs (e.g. St John's wort, echinacea, kava and garlic) and natural compounds isolated from herbs (e.g. flavonoids, coumarins, furanocoumarins, anthraquinones, caffeine and terpenes) have been identified as substrates, inhibitors and/or inducers of various CYP enzymes [18]. Specifically, clinical studies have shown that long-term (2 weeks) St John's wort administration significantly induced intestinal and hepatic CYP3A4 and possibly other CYP enzymes involved in drugs metabolism [19–26]. Moreover, a clinical study performed on 12 healthy subjects showed that echinacea modulated the catalytic activity of CYP3A at hepatic and intestinal sites (induction of hepatic CYP3A4 and inhibition of intestinal CYP3A4) [27]. By contrast, a number of herbal medicines, including green tea [28], ginkgo [29], garlic [30] saw palmetto [31] and Siberian ginseng [32] did not affect CYP3A4 and CYP2D6 activities in normal volunteers.

P-glycoprotein in the intestine, liver and kidney may play an important role in the absorption, distribution, or excretion of drugs. P-glycoprotein appears to limit the cellular transport from intestinal lumen into epithelial cells and also enhances the excretion of drugs out of hepatocytes and renal tubules into the adjacent luminal space [33]. Like CYP, P-glycoprotein is vulnerable to inhibition, activation, or induction by herbs and herbal constituents. Curcumin, ginsenosides, piperine, sylimarin and catechins may affect P-glycoprotein-mediated drug transport [17]. St John's wort induces the intestinal expression of P-glycoprotein [34–36] both in isolated cells [35] and in healthy volunteers [34,36]. Hyperforin, a major ingredient of St John's wort, binds to orphan pregnane X receptor [37,38] resulting in a series of intracellular events leading to the expression of CYP3A4

and P-glycoprotein [16]. A few pharmacodynamic interactions have also been described. Pharmacodynamic interactions may be additive (or synergetic), whereby the herbal medicine potentiates the action of synthetic drugs (e.g. interaction between the anticoagulant warfarin with antiplatelet herbs), or antagonistic, whereby the herbal medicine reduces the efficacy of synthetic drugs (e.g. kava possesses dopaminergic antagonistic properties and hence might reduce the pharmacological activity of the anti-parkinson drug levodopa) [15].

LIMITATIONS

Much of the available information about the interaction between herbal products and prescribed drugs is gleaned from case reports, although clinical studies are now also beginning to appear in the literature. The published case reports are often incomplete as they do not allow us to conclude that a causal relationship exists. Even documented case reports have to be interpreted with great caution, as causality is not usually established beyond reasonable doubt. According to the scoring system described by Fugh-Berman and Ernst [7], 68.5% of the cases reported were classified as 'unevaluable' (i.e. reports contained inadequate information to assess the likelihood of an interaction), 18.5% were classified as 'possible' (i.e. reports provided some evidence for an interaction, but there may be other causes of the event) and 13% as 'well documented' (reports appeared to provide reliable evidence for an interaction).

INTERACTIONS WITH CARDIOVASCULAR PHARMACOTHERAPY

Interaction between herbal remedy and conventional cardiovascular drugs is a potentially important safety issue, particularly for patients taking anticoagulants. The majority of reports concern drugs with a narrow therapeutic index such as warfarin and digoxin. These interactions have been systematically reviewed [10] and summarized here in *Table II*.

Interactions with anticoagulant drugs

Warfarin owes its action to its ability to antagonize the cofactor function of vitamin K. Theoretically, increased anticoagulant effects could be expected when warfarin is combined with coumarin-containing herbs (e.g. boldo, fenugreek, don quai) or with antiplatelet herbs (e.g. danshen, garlic, ginkgo) [10]. Naturally occurring

Table II Clinical interactions between herbal medicines and conventional cardiovascular drugs.

Drug	Herb	Result of interaction	Possible mechanism	Clinical comment	Source of evidence	Reference
Digoxin	Gum guar, St John's wort, wheat bran	Decreased plasma digoxin concentration	*Multiple mechanisms:* (i) gum guar delays gastric emptying and hence may reduce digoxin absorption (ii) St John's wort induces P-glycoprotein which is involved in digoxin absorption/excretion (iii) Fibres in bran may trap digoxin in the gut	Digoxin has a narrow therapeutic index	Clinical studies	66–69
Aspirin	Ginkgo	Spontaneous hyphema	Additive effect on platelet aggregation (ginkgolides have antiplatelet activity)	Hyphema is a clinical rare problem	A case report	143
Lovastatin	Pectin or oat bran	Decreased absorption of lovastatin	Pectins or bran fibres may bind or trap lovastatin in the gut	The therapeutic manifestation of this interaction remains to be determined	A clinical study	75
Simvastatin	St John's wort	Decreased plasma digoxin concentration	Simvastatin is a substrate of P-glycoprotein and is metabolized by CYP enzymes. Both CYP enzymes and P-glycoprotein are induced by St John's wort	The therapeutic manifestation of this interaction remains to be determined	A clinical study	74
Phenprocoumon	Ginger	(i) Over-anticoagulation	(i) Additive effect on coagulation (ginger inhibits platelet aggregation)	The patient developed an elevated INR and epistaxis	A case report	65
	St John's wort	(ii) decreased anticoagulant effect	(ii) Phenprocoumon is metabolised by cytochrome enzymes which are induced by St John's wort	Phenprocoumon has a narrow therapeutic index	A clinical study	64,67
Verapamil	St John's wort	Decreased bioavailability of verapamil	Induction of intestinal CYP3A4 by St John's wort	The clinical significance remains to be determined	A clinical study	26
Warfarin	(i) Boldo/fenugreek, curbicin, cranberry danshen, devils claw, dong quai, garlic, ginkgo, ginseng, Chinese wolfberry, mango, papaya, quilinggao, PC-SPES	(i) Over-anticoagulation	(i) In general, additive effects on coagulation mechanisms. Such herbs may have anticoagulant (boldo, fenugreek, don quai, PC-SPES) or antiplatelet (i.e. danshen, garlic, ginseng, ginkgo) properties. Other mechanisms include: cranberry flavonoids may inhibit CYP enzymes responsible of warfarin metabolism; curbicin contain high amount of vitamin E which can antagonize vitamin K. Mechanism not known for devils claw, quilinggao and Chinese wolfberry	(i) Risk of bleeding. Given the narrow therapeutic index of warfarin, vigilance is needed. Caution for ginkgo (a case reported intracerebral haemorrhage) and cranberry (fatal haemorrhage)	(i) Single case reports for boldo/fenugreek, devil's claw, ginkgo, ginseng, Chinese wolfberry, papaya, PC-SPES. Multiple case for cranberry curbicin, danshen, dong quai, garlic	40–53,61
	(ii) Ginseng[a], green tea, soya, St John's wort	(ii) Decreased anticoagulant effect	(ii) Green tea contain vitamin K and thus may antagonize the effect of warfarin; warfarin is metabolized by CYP enzymes which are induced by St John's wort. Mechanism not known for ginseng and soya	(ii) Potential thrombotic complications	(ii) Single case reports for green tea, ginseng and soya. Multiple cases for St John's wort. A clinical study for ginseng and St John's wort	54–58,60,62,63

coumarins are only weak anticoagulant, but if the plant material is not stored properly dicoumarol may be formed by microbial transformation, and this compound is much more potent [1,39]. Conversely, vitamin K containing herbs (e.g. green tea) can antagonized the anticoagulant effect of warfarin. Case reports indicate over-anticoagulation [generally revealed by increased international normalized ratio (INR) values] when warfarin is combined to boldo/fenugreek [40], curbicin (a preparation containing saw palmetto, pumpkin and vitamin E, see *Table I*) [41], danshen [42–44], devil's claw [45], dong quai [46,47], garlic [48], ginkgo [49], Chinese wolfberry (Go-Qi-Zi) [50], papaya [45], mango [51], PC-SPES (a mixture of eight herbs) [52], quilinggao (a Chinese herbal combination) [53] and decreased anticoagulant effect when the drug is co-administered with cranberry [54,55], green tea [56], soya [57] and St John's wort [58]. Analysis of case reports revealed reliable evidence for an interaction only for the boldo/fenugreek, danshen, cranberry, dong quai and ginkgo interactions; some evidence for an interaction (but there may be other causes of the event) was provided for curbicin, quilinggao, mango, Chinese wolfberry, green tea, PC-SPES and soya, while warfarin interactions caused by devil's claw, papaya and garlic were published in reports containing inadequate information to assess the likelihood of an interaction [7]. PC-SPES has been found to contain adulterated indomethacin, warfarin and diethylstilbestrol [59]. In 2003, it has been suspended from sale from the FDA [9].

A case of fatal interaction has been also reported [54]. Six weeks after starting cranberry juice a 70-year-old man under warfarin was admitted to hospital with an INR >50. Before, his control of INR had been stable. He died of a gastrointestinal and pericardial haemorrhage. Moreover, the Committee on Safety of Medicines (UK) reported seven other reports about a possible interaction between warfarin and cranberry juice leading to changes in INR or bleeding [55]. Cranberry juice contains antioxidants, including flavonoids, which are know to inhibit CYP enzymes responsible of warfarin metabolism [16,18].

The reported ginseng–warfarin interaction is somewhat puzzling as case reports have shown that the herb may either decrease [60] or increase [61] the anticoagulant effect of warfarin. Two recent randomized clinical trials have investigated the effect of ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects [62,63]. Jiang et al. showed a 7-day treatment with ginseng (*Panax ginseng*) did not

affect the pharmacokinetics or pharmacodynamics (platelet aggregation and INR) of the anticoagulant in healthy subjects [62]; by contrast, Yuan et al. reported that the administration of American ginseng for 2 weeks reduced warfarin's anticoagulant activity (decreased INR and warfarin AUC) [63]. The use of different species (*Panax ginseng* vs. *Panax quinquefolius*) and a different time of administration (1 week vs. 2 weeks) may explain such apparent discrepancy.

Phenprocoumon is an anticoagulant chemically related to warfarin. A clinical study [64] highlighted the possible reduced efficacy of this anticoagulant if coadministered with St John's wort. Another clinical trial showed that coadministration of St John's wort increased the apparent clearance of warfarin, leading to a reduction in the pharmacodynamic effect of the anticoagulant [62]. Consistently, seven cases of INR associated with concomitant use of warfarin and St John's wort were reported by the Swedish Medical Product Agency [58]. Lastly, a 76-year-old woman on long-term phenprocoumon therapy developed an elevated INR and epistaxis after taking the herb ginger. The INR returned to the normal range after ginger was stopped and vitamin K1 given [65]. An objective causality assessment revealed that the adverse drug event as a result of the phenprocoumon and ginger interaction was probable.

Interactions with cardiac inotropic drugs

There is clinical evidence that blood levels of digoxin can be reduced by the concurrent administration of some herbal products, although to date, no therapeutic interactions between herbs and digoxin have been reported. St John's wort was shown to reduce digoxin through level after 10 days of co-medication in a single-blind, placebo-controlled study [66]. It was suggested that the underlying mechanism involves induction (by St John's wort) of the P-glycoprotein drug transporter, facilitating the efflux of the drug from the enterocytes to the intestinal lumen [18]. The interaction between St John's wort and digoxin seems to be correlated with the dose, particularly of the active ingredient hyperforin [67]. Other clinical trials showed that serum digoxin concentration may be reduced by concomitant administration of gum guar (which may reduce digoxin absorption by delaying gastric emptying) [68] or whet bran (digoxin may be trapped by fibres contained in wheat bran) [69]. However these interactions have likely no clinical relevant influence on therapeutic digoxin [10]. By contrast, two herbal medicines, namely hawthorn and ginkgo, did not change the pharmacokinetics

of orally administered digoxin in healthy volunteers [70,71].

Increased levels of digoxin have been associated with ingestion of Siberian gingeng [72]. The patient was asymptomatic for digoxin toxicity despite a level of 5.2 ng/mL. Siberian ginseng contains glycosides with structural similarities to digoxin which interfere with digoxin assay [73].

Interactions with antihyperlipidaemic drugs

Simvastatin, pravastatin and lovastatin are inhibitors of hydroxymethylglutaryl (HMG)-CoA reductase, the rate limiting step in cholesterol synthesis. Two clinical studies reported in a single publication showed that St John's wort decreased plasma concentrations of simvastatin but not of pravastatin [74]. The difference probably lies in the different metabolic profiles of the two drugs. Simvastatin, in contrast to pravastatin, is metabolized through a CYP-dependent pathway, and it is also a substrate of P-glycoprotein. The therapeutic manifestation of this interaction remains to be determined.

A decrease of absorption of lovastatin [associated to increased low-density lipoprotein (LDL) levels] was observed in patients who took this drug concomitantly with pectin or oat bran [75]. Lovastatin pharmacokinetics and LDL returned normal after bran discontinuation. The interaction is likely due to the ability of pectins or bran fibres to bind or trap concurrently administered lovastatin.

Interactions with antihypertensive drugs

Few (and poorly documented) cases of herb–drug interactions with antihypertensive drugs have been reported. Surprisingly, an elderly patient was found to have an increase in blood pressure after taking ginkgo (a peripheral vasodilator) while receiving a thiazide diuretic (not specified in the original paper) [45]. There is no rational pharmacological mechanism to explain this unusual interaction. In addition, hypokalemia, associated to flaccid quadriplegia, has been reported after the ingestion of small amounts of liquorice (which possess mineralcorticoid effects) in combination with antihypertensive treatment (not specified in the original paper) [76].

Verapamil reduces arterial pressure by inhibiting calcium ion influx into the vascular smooth muscle cells, which results in a decrease in smooth muscle tone and vascular resistance. Tannergreen et al. [26] reported that repeated administration of St John's wort decreased verapamil bioavailability in healthy volunteers. This effect is likely caused by induction of first-pass CYP3A4

metabolism in the gut, because the jejunal permeability and the terminal half-life of verapamil were unchanged. In addition, verapamil is also a substrate of P-glycoprotein [77], which can be induced by St John's wort [16,37,38].

INTERACTIONS WITH DRUGS AFFECTING THE CENTRAL NERVOUS SYSTEM

The interactions between herbal remedies and conventional drugs affecting the central nervous system are summarized in *Table III*. Patients mixing synthetic and herbal anxiolytic or antidepressant drugs are at the highest risk.

Interactions with antidepressant drugs

The herb St John's wort is effective in the treatment of mild to moderate depression [24]. Both St John's wort and synthetic antidepressants have a high probability of concomitant use. St John's wort and serotonin re-uptake inhibitors (i.e. sertraline, paroxetine, nefazodone and venlafaxine) may result in symptoms characteristic of central serotonin excess (e.g. mental status changes, tremor, autonomic instability, gastrointestinal upset, headache, myalgias and motor restlessness) as highlighted by case series and case reports [78–80]. These effects could be the result of an additive effect on 5-hydroxytryptamine (5-HT) because hyperforin in St John's wort inhibit the re-uptake of several brain neurotransmitters including 5-HT [24]. Concomitant use of St John's wort and sertraline has been reported to cause a manic episode in a 28-year-old man [81]. According to the report reliability scale for drug interaction [7], the case was classified as possible, although it was complicated by concomitant testosterone replacement therapy following bilateral orchidectomy. Finally, a clinical study showed that co-medication with St John's wort decreased plasma and urine concentration of amitriptyline in 12 patients [82]. In addition to being a P-glycoprotein substrate, the demethylation and subsequent hydroxylation of amitriptyline is catalysed by CYP2C19 and CYP3A4 which may be induced by St John's wort.

Other herbs which may interact with conventional antidepressants include ginkgo and ginseng. A 80-year-old woman with Alzheimer's disease fell into a coma after taking a low dose of the atypical antidepressant trazodone with ginkgo [83]. The case was classified as 'possible' [7]. Another report described a patient who experienced insomnia, headache, tremulousness and

Table III Clinical interactions between herbal medicines and conventional drugs affecting the central nervous system.

Drug	Herb	Result of interaction	Possible mechanism	Clinical comment	Source of evidence	Reference
Alprazolam	St John's wort	Decreased plasma levels of alprazolam	Alprazolam is a specific probe for CYP 3A4, which is induced by St John's wort	The therapeutic manifestation of such interaction was not determined	Clinical studies	23,25
	Kava	Semicomatose state	Additive effect on GABA receptors. Moreover, kava inhibits CYP3A4 in humans	The patient was lethargic and disoriented for several hours	A case report	93
Amitriptyline	St John's wort	Decreased plasma levels of amitriptyline	Amitriptyline is a substrate of both CYP2C19 and P-glycoprotein which are induced by St John's wort	The clinical significance of such interaction was not determined	A clinical study	82
Buspirone[a]	St John's wort	Hypomania	Synergistic effect on 5-HT receptors	This is the first case of hypomania following brain injury involving herb–drug interaction	A case report	95
Caffeine	Echinacea	Reduction of caffeine oral clearance	Caffeine is a substrate of CYP1A2 which is inhibited by echinacea	This interaction is not clinically relevant	A clinical study	27
Fluphenazine	Evening primrose oil	Seizures	Gamalenic acid from evening primrose oil lowers the seizure threshold	Phenothiazines are known to be epileptogenic themselves	Two cases in a clinical study	90
Levodopa	Kava	Reduced efficacy of levodopa	Kava possesses dopaminergic antagonistic properties	Increase in the duration and number of 'off' periods have been reported	A case report	97
Lithium	(i) Psyllium, hispagula	(i) Decreased plasma lithium concentration	(i) Hydrophilic psyllium may prevent lithium from ionizing	The therapeutic index of lithium salts are extremely low	A case report	86
	(ii) Herbal diuretics[b]	(ii) Decreased plasma lithium concentration	(ii) Unknown		A case report	87
Midazolam	Echinacea	Increased (oral midazolam) or decreased (systemic midazolam) clearance	Midazolam is a substrate of CYP3A4. Echinacea inhibits intestinal CYP3A4, while it induces hepatic CYP3A	The therapeutic manifestation of such interaction was not determined	A clinical study	27
	St John's wort	Decreased plasma levels of midazolam	Induction of CYP3A4 by St John's wort	The therapeutic manifestation of such interaction was not determined	Clinical studies	20,22,36
Phenelzine	Ginseng	Sleeplessness, tremor and headaches	Unknown	The psychoactive effects were considered to be relevant	Two cases	84
Phenytoin	Shankhapushpi	Loss of seizure control	Not know	The interaction is potentially relevant	Two cases	91
Procyclidine	Betel nut	Rigidity, bradykinesia, jaw tremors	Antagonistic effect of arecoline from betel nut to the anticholinergic agent procyclidine	Betel nut may reduce drug compliance in schizophrenic patients	A case report	88
SRI[c]	St John's wort	Serotonergic syndrome	Synergistic effect on 5-HT uptake	The syndrome could be fatal, particularly in elderly	Case series and case reports	78–80
Trazodone	Ginkgo	Coma	Not known	The interaction is potentially relevant	A case report	83

[a]A case of possible serotonergic syndrome has been also reported [96].
[b]The herbal formulation contained juniper, buchu, horsetail, corn silk, bearberry, parsley, bromelain and paprika.
[c]Serotonin-reuptake inhibitors (i.e. sertraline paroxitine, nefazodone and venlafaxine). A case of mania in a patient taking St John's wort and sertraline has been also reported [81].

mania after co-administration of ginseng with phenel-zine [84]; here, causality is likely because inadvertent re-challenge resulted in similar symptoms [85]. The mechanisms of such interactions are not known.

Interactions with neuroleptic drugs

Lithium salts are used prophylactically in treating manic-depressive patients and in the treatment of manic episodes. Patients taking isphagula or psyllium were found to have lower blood levels of lithium, possibly because the plant product may trap lithium in the gut [86]. In addition, a 26-year-old woman stable on lithium for 5 months, experienced dizziness, grogginess and diarrhoea after taking a combination of herbal diuretics (juniper, buchu, horsetail, corn silk, bearberry, parsley, bromelain and paprika) [87]. The adverse events were associated to increased plasma lithium levels. As there were several herbal diuretics in the preparation used and the mechanism of action of each is elusive, it is impossible to determine which herb caused the lithium toxicity.

Extrapyramidal symptoms occurring in a schizophrenic patient who was maintained on depot neuroleptic medication following a period of heavy betel nut are described in a well-documented case report [88]. The underlying mechanism of this interaction is based on the pharmacological antagonism of the anticholinergic agent procyclidine (which is given to treat acute neurological adverse effects resulting from the use of neuroleptic drugs) by arecoline (an acetylcholine receptor agonist), the active ingredient of the betel nut [89].

Seizures were reported in two patients taking the phenothiazine fluphenazine with evening primrose oil and in one patient taking placebo with evening primrose oil in a study of 23 patient with schizophrenia [90]. Evening primrose oil contains γ-linolenic acid, which lowers the seizure threshold [34]. However, it should be noted that phenothiazines are known to be epileptogenic themselves.

Interactions with antiepileptic drugs

During the course of routine plasma drug level monitoring an unexpected loss of seizure control and reduction in plasma phenytoin levels was noticed in two patients who were also taking the Ayurvedic multi-herb syrup Shankhapushpi [91]. Subsequent animal experiments confirmed that the herbal remedy decreased the anti-epileptic activity of phenytoin without lowering its plasma level [91]. The mechanism of this interaction is not known. In addition, a clinical study showed that a

14-day treatment with St John's wort did not alter carbamazepine pharmacokinetics in healthy volunteers [92].

Interactions with anxiolytic drugs

The benzodiazepines alprazolam and midazolam are used experimentally as probe for CYP3A4 activity because they are entirely metabolized by intestinal and hepatic CYP 3A4. Consistently, clinical studies have shown that St John's wort decreased alprazolam and midazolam plasma levels in healthy volunteers [20,22,23,25,36]. St John's wort decreased plasma levels of midazolam the effect being considerably less after intravenous administration than after oral administration. These findings indicate that enzymatic induction occurs both in the intestine and in the liver [36]. Moreover, a clinical study performed on 12 healthy subjects showed that echinacea increased the oral availability of midazolam (CYP3A probe), which is consistent with inhibition of intestinal CYP3A by the herb. By contrast the AUC of systemically given midazolam was reduced possibly due to induction of hepatic CYP3A [27]. The increase of oral availability of midazolam by echinacea mainly based on the inclusion of the reduced AUC of midazolam after intravenous dosing in the calculation of oral availability [27]. In addition, clinical studies showed the pharmacokinetics of alprazolam were not affected by a number of herbal medicines, including green tea, saw palmetto, garlic, ginkgo and Siberian ginseng [28–32].

A poorly documented [7] case report described a semicomatose state in a patient taking kava and alprazolam [93]. Kava inhibits human CYP activities [94] and thus it might increase alprazolam plasma concentrations. Moreover, a pharmacodynamic mechanism cannot be excluded as both kava and benzodiazepines interfere with GABA receptors [5].

Another anxiolytic drug which can interact with herbal medicines is buspirone, a 5-HT1A receptor agonist. Dannawi et al. reported a case of a possible serotonin syndrome after combination of buspirone and St John's wort [95]. An additive effect on 5-HT receptors (St John's wort inhibit 5-HT re-uptake) [8,24] may explain such interaction. Moreover a female patient experienced hypomania after adding St John's wort and ginkgo to her regimen of buspirone [96].

Interactions with anti-parkinson drugs

Levodopa is a metabolic precursor of dopamine. An increase in the duration and number of 'off' periods in a patient with Parkinson's disease treated with levodopa

has been reported [97]. The assessors of this report suggest that causality is likely [7]. Kava possess dopamine receptor antagonistic properties [97,98] which could explain the reduced efficacy of levodopa.

INTERACTIONS WITH ORAL CONTRACEPTIVES

Drugs that induce CYP3A enzymes, such as rifampicin, have been associated with reduced efficacy of oral contraceptives and breakthrough bleeding [99]. This interaction is thought to reflect the significant contribution of CYP3A enzymes to the oxidative metabolism of 17α-ethinyl estradiol and norethindrone [100]. Recently, there have been case reports of breakthrough bleeding in women who were stabilized by use of ethinyl estradiol/desogestrel containing oral contraceptives after co-administration of St John's wort [58,101]. This adverse event was confirmed by two clinical trials performed in healthy female volunteers, who showed a higher incidence of intracyclic bleeding episodes after co-administration of St John's wort and an oral contraceptive (ethinyl estradiol and norethindrone) [22,102]. Most importantly, some reports of women becoming pregnant whilst using oral contraceptives and St John's wort have been reported by UK (seven cases), German (four cases) and Swedish (two cases) authorities [103]. These cases were followed by a further detailed report of unwanted pregnancy in a depressed 36-year-old woman [104]. Clinical studies designed to elucidate the mechanism of these interactions have shown that St John's wort (consistent with increased CYP3A4 activity), may decrease plasma levels of norethindrone and 3-ketodesogestrel, as well as the half-life of elimination of ethynyl estradiol [22,102]. Although the number of bleeding episodes increased during co-medication with St John's wort, it is worth noting that the anti-ovulatory effect was not impaired by co-medication with the herb [102].

INTERACTIONS WITH IMMUNOSUPPRESSANTS

The interaction between cyclosporine and St John's wort is one of the most serious, and potentially fatal, interaction between a herbal remedy and a conventional drug. It is also one of the most well documented, with multiple case reports and case series reported [105–114]. The common clinical features of these cases are that heart, renal or liver transplant patients stabilized on cyclosporine showed decreased plasma levels (associated,

in some cases, with acute rejection episodes) after taking St John's wort at therapeutic dosage. The clinical picture improved in all cases following discontinuation of the herbal remedy. Cyclosporine is a substrate of P-glycoprotein and metabolized by CYP3A4. St John's wort may thus decrease intestinal absorption and increase the metabolism of cyclosporine.

A case of rhabdomyolysis in a stable renal-transplant recipient, attributed to red yeast rice has been described [115]. The condition resolved when consumption of the herbal product ceased. The authors postulated that the interaction of cyclosporine and the herbal product through the CYP system resulted in the adverse effect. Red yeast rice contains monacolins, including monacolin K, which is identical to lovastatin.

Another herb that may interact with cyclosporine is red avens (*Geum chiloense*) [116]. Cyclosporine plasma levels in a 54-year-old renal transplant patient abruptly increased (469–600 mg/dL) after taking red avens. Blood levels returned to 55 mg/dL on cessation of this herb.

Finally, two clinical trials [117,118] showed that co-administration of St John's wort dramatically decreased the AUC of tacrolimus. Tacrolimus undergoes extensive hepatic metabolism mainly by CYP3A4 and is also a substrate for P-glycoprotein. Tacrolimus undergoes extensive hepatic metabolism mainly by CYP 3A4 and is also a substrate for P-glycoprotein.

INTERACTIONS WITH ORAL HYPOGLYCAEMIC DRUGS

Dietary gums (e.g. gum guar) are advocated to reduce postprandial hyperglycaemia [1]. Because of their effect on prolonging gastric retention and because drugs will diffuse more slowly out of viscous matrices than from solutions, gums may affect the absorption of concomitantly administered drugs, including hypoglycaemic drugs [119]. Clinical studies have shown that gum guar reduced the absorption of metformin [120] and glibenclamide (gliburide) [121] but not glipizide [122] to a clinical significant degree. By contrast, another trial showed that gum guar enhanced the insulinogenic and blood glucose lowering effect of glibenclamide [123].

A fall in glucose levels has been reported in a 40-year-old diabetic woman taking chlorpropamide and a carry containing garlic and karela [124]. This event is likely because of an additive effect on glucose level, as both garlic and karela possess hypoglycaemic effects [1].

INTERACTIONS WITH CHEMOTHERAPEUTIC DRUGS

By using a urinary excretion method, the bioavailabilities of ampicillin and amoxicillin were determined in eight healthy volunteers [125] after khat chewing. Drugs were given at various time before khat chewing session. The extent and rate of ampicillin bioavailability were reduced significantly by khat chewing except when administered 2 h after the khat chewing session. The mechanisms of this interaction are unknown. It has been proposed that ampicillin combines with khat tannins to form an insoluble and poorly absorbed complex [89].

Another double blind trial, performed on 10 healthy volunteers, showed that the peak penicillin concentration and the AUC were reduced by co-administration of gum guar [126]. This interaction is not clinically relevant, especially in view of the fact that oral penicillin V should always be taken on an empty stomach.

The effect of the Chinese medicines Shosaiko-to (TJp), Rikkunshi-to (TJ-43) and Sairei-to (TJ-114) on the bioavailability of the urinary tract antiseptic ofloxacin has been evaluated in seven healthy volunteers [127]. It was found that these Chinese medicines had no significant effect on the rate and extent of bioavailability of ofloxacin.

Clinical studies have shown that St John's wort reduced plasma concentration of the antiretroviral drugs indinavir (a protease inhibitor) [128] and the oral clearance of the non-nucleoside reverse transcriptase inhibitor nevirapine (a non-nucleoside reverse transcriptase inhibitor) [129]. These results have important clinical implications for HIV-infected patients as low plasma concentrations of antiretroviral drugs are a cause of drug resistance and treatment failure. It is important to point out that other antiretroviral drugs are also metabolized by the CYP3A4 isoform and thus may be adversely influenced by concomitant intake of St John's wort [130]. By contrast, clinical studies have shown that some herbs, including goldenseal (*Hydrastis canadensis*) [131] and milk thistle [132] do not affect the pharmacokinetics of indinavir in healthy volunteers; in addition, acute dosing of garlic over 4 days did not significantly alter the single-dose pharmacokinetics of the protease inhibitor ritonavir [133].

A significant decline in the plasma concentrations of the protease inhibitor saquinavir was observed in 10 healthy volunteers after repeated administration of garlic [134]. On the basis of AUC, C_{max} and C_8 values, the authors suggest that garlic affected the bioavailability of saquinavir rather than its systemic clearance. The effect may be caused, at least in part, by induction of CYP450 in the gut mucosa by garlic. Indeed, administration of garlic for 5 days led to a significant increase in CYP450 activity in rats [135], although this finding has not been confirmed in humans [30].

Irinotecan, employed mainly for the treatment of cancer of the colon or rectum, is a pro-drug of SN-38 and a known substrate for CYP3A4. A randomized, non-blinded cross-over study showed that St John's wort decreased plasma levels of the active metabolite of SN-38 by 42% in five cancer patients. Consequently, the degree of myelosuppression was substantially worse in the absence of St John's wort [136].

INTERACTIONS WITH ANTIASTHMATIC/ ANTIALLERGIC/ANTI-INFLAMMATORY DRUGS

There is some indirect evidence in the literature that liquorice may interact with prednisolone. Chen et al. [137] showed that oral glycyrrhizin (a major constituent of liquorice) increased the plasma prednisolone concentrations in six healthy men. Glycyrrhizin, which is a strong inhibitor of 11 beta-hydroxysteroid dehydrogenase (the enzyme which catalyses the conversion of cortisol to the inactive steroid cortisone), influences prednisolone pharmacokinetics by inhibiting its metabolism. Moreover, three major traditional Chinese medicines (Sho-saiko-To, Saiboku-To, and Sairei-To) containing glycyrrhizin affected prednisolone pharmacokinetics in healthy volunteers [138]. As these herbal mixtures had different effects on prednisolone concentrations, it is unlikely that glycyrrhizin alone may explain these differences on prednisolone kinetics.

One case of a reduction in plasma theophylline concentrations associated with St John's wort treatment has been reported [139]. This resulted in an increased dosage of theophylline to achieve therapeutic concentration. The same study also reported in vitro evidence that components of St John's wort induced hepatic enzymes. This report provided some evidence for an interaction, but there may be other causes involved [7]. However, a recent randomized clinical trial showed that a 15-day treatment with St John's wort did not alter the pharmacokinetics of theophylline in 20 healthy volunteers [140].

An open-label study showed that single administration of St John's wort increased, while a 14-day treatment decreased, plasma levels of fexofenadine, a non-sedating H1-receptor antihistaminic drug [141]. As fexofenadine

is a selective probe drug to determine P-glycoprotein activity, the authors hypothesized that acute St John's wort inhibited, where as long-term treatment induced intestinal P-glycoprotein.

Ginkgo constituents (ginkgolides and others) have antiplatelet activity and are platelet activating factor (PAF) receptor antagonists [142]. Case reports demonstrate that patients taking a number of non-steroidal anti-inflammatory drugs, including aspirin [143], ibuprofen [144] and the cyclo-oxygenase-2 inhibitor rofecoxib [145] experienced severe bleeding after self-prescribing ginkgo at recommended doses. Adverse events were particularly severe for aspirin (spontaneous hyphema) [143] and for ibuprofen (comatose state with an intra-cerebral mass bleeding of which the patient died) [144]. In addition, aspirin plasma concentrations may be increased by concomitant use of tamarind [146], a food also used as a herbal medicine.

A clinical trial suggests that garlic changes some pharmacokinetic variables of paracetamol (acetaminophen) after 1–3 months of treatment [147]. Specifically, it was found that commercial aged garlic extract (approximately equivalent to six to seven cloves of garlic) had no effect on oxidative metabolism, but caused a slight increase in sulphate conjugation of the drug. The precise mechanisms and the clinical significance of this interaction are presently not known.

Lastly, it has been shown that the half-life of phenazone (antipyrine) was not affected by ginkgo treatment, whereas it was significantly decreased after phenytoin treatment in healthy volunteers [148].

MISCELLANEOUS INTERACTIONS

A brief episode of acute delirium, possibly induced by exposure to St John's wort, valerian and the antidiarrhoeal opiate loperamide has been reported [149]. The case provided some evidence for interaction, but there may be other causes of the event [7]. The mechanisms of this interaction are not known.

A randomized, cross over study, performed on 12 adult men showed that St John's wort induced both CYP3A4-catalysed sulphoxidation and CYP2C19-dependent hydroxylation of omeprazole and enormously decreased its plasma concentration [150]. The author believe that an adjustment of the dose should be made to safeguard successful omeprazole therapy when co-administration with St John's wort.

A reduction of methadone plasma levels has been reported in four addict patients after St John's wort intake [151]. Two patients reported symptoms that suggested a withdrawal syndrome. The authors suggest that such interaction, if not correctly identified and handled, might cause unnecessary discomfort to the patient, lead to resumption of illicit drug use, or be a risk factor for discontinuation of the methadone or antidepressant treatment.

CONCLUSIONS

There is evidence that taking herbal preparations can result in pharmacokinetic or pharmacodymnamic interactions that represent a potential risk to patients taking conventional medicines. The pharmacokinetic interactions that have been identified so far all point towards the fact that herbs induce CYP enzymes and P-glycoprotein. The majority of interactions identified to date involve medicines that require regular monitoring of blood levels (e.g. warfarin, cyclosporine). Given that the number of medicines that currently require monitoring is low, compared with the number of medicines that are metabolized by CYP enzymes, it is highly likely that further interactions will be identified.

Although some herb–drug interactions may be clinically insignificant (e.g. interaction between gum guar and penicillin V), others may have serious consequences (e.g. interaction between St John's wort and cyclosporine). Potentially, this concerns a very long list of medicinal herbs [14]. The subject clearly requires more research, which, in turn, begs the question who should fund such research? A recent survey indicates that neither the pharmaceutical nor the herbal industry is inclined to take on this responsibility [152]. Knowing that millions of patients take herbal and conventional medicines concomitantly, often without the knowledge of their physicians, and considering our present lack of understanding of herb–drug interactions, more research into this area seems a matter of urgency.

ACKNOWLEDGEMENTS

NOTE ADDED IN PROOF

Dresser and colleagues (2002) have shown that peppermint oil increased the area under the curve values and the peak plasma concentration of felodipine in humans [153].

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