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# Interactions between Herbs and Conventional Drugs: Overview of the Clinical Data

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**Key Words**

Complementary medicine · Cytochrome P · Dietary supplements · Drug interaction · Herbal medicine · P-glycoprotein · Traditional Chinese medicine · Safety of herbal products · St. John's wort

**Abstract**

This article provides an overview of the clinical evidence of interactions between herbal and conventional medicines. Herbs involved in drug interactions – or that have been evaluated in pharmacokinetic trials – are discussed in this review. While many of the interactions reported are of limited clinical significance and many herbal products (e.g. black cohosh, saw palmetto, echinacea, hawthorn and valerian) seem to expose patients to minor risk under conventional pharmacotherapy, a few herbs, notably St. John's wort, may provoke adverse events sufficiently serious to endanger the patients' health. Healthcare professionals should remain vigilant for potential interactions between herbal medicines and prescribed drugs, especially when drugs with a narrow therapeutic index are used. 

## Introduction

According to the World Health Organisation, herbal medicines are defined as 'finished, labelled medicinal products that contain as active ingredients aerial or underground parts of plants, or other plant material, or combinations thereof, whether in the crude state or as plant preparations. Plant material includes juices, gums, fatty oils, essential oils, and any other substances of this nature. Herbal medicines may contain excipients in addition to the active ingredients. Medicines containing plant material combined with chemically defined active substances, including chemically defined, isolated constituents of plants, are not considered to be herbal medicines' [1]. Thus, herbal medicines contain a combination of pharmacologically active plant constituents that are claimed to work synergistically to produce an effect greater than the sum of the effects of the single constituents [2–5]. There is a general belief by the public that herbal medicines are safe because they are natural. However, this is a hazardous oversimplification. Many different side effects to herbs have been reported and recently reviewed [6, 7], including adverse events caused by herb-to-drug interactions [6–8]. Since all herbal medicines are mixtures of more than one active ingredient, such combinations of many substances obviously increase the like-

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lihood of interactions taking place. Hence, theoretically, the likelihood of herb-to-drug interactions is higher than drug-to-drug interactions, if only because synthetic drugs usually contain single chemical entities.

The aim of this article is to provide an overview of the clinical data regarding the interactions between herbal remedies and prescribed drugs. Detailed considerations on the mechanisms and molecular explanations of the clinical observations of herb-to-drug interactions can be found elsewhere [9–11]. The herbal remedies involved in clinical herb-to-drug interactions are given in table 1, which also reports the level of evidence for each interaction. The ultimate goal of this article is to raise the awareness of pharmacists and physicians regarding this topic and thus protect the health of consumers.

## Mechanisms of Herb-to-Drug Interactions: General Considerations

Herb-to-drug interactions are based on the same pharmacokinetic (changes of plasma drug concentration) and pharmacodynamic (drugs interacting at receptors on target organs) principles as drug-to-drug interactions.

The pharmacokinetic interactions that have been identified so far all point towards the fact that a number of herbs, most notably St. John's wort, can affect the blood concentration of different conventional medicines that are metabolized by cytochrome P450 (CYP, the most important phase I drug-metabolizing enzyme system) and/or are transported by P-glycoprotein (a glycoprotein which influences drug absorption and elimination by limiting the cellular transport from the intestinal lumen into epithelial cells and by enhancing the excretion of drugs from hepatocytes and renal tubules into the adjacent luminal space). Polymorphisms in the genes for CYP enzymes and P-glycoprotein may influence the interactions mediated through these pathways [12]. Probe drugs used in pharmacokinetic trials include midazolam, alprazolam, nifedipine (CYP3A4), chlorzoxazone (CYP2E1), debrisoquine, dextromethorphan (CYP2D6), tolbutamide, diclofenac and flurbiprofen (CYP2C9), caffeine, tizanidine (CYP1A2) and omeprazole (CYP2C19). Fexofenadine, digoxin and talinolol have been extensively used in pharmacokinetic trials as P-glycoprotein substrates.

Pharmacodynamic interactions have been less studied but may be additive (or synergetic), i.e. the herbal medicines potentiate the pharmacological/toxicological action of synthetic drugs, or antagonistic, i.e. the herbal medicines reduce the efficacy of synthetic drugs. Warfarin interactions are a classical example of pharmacodynamic interactions. Theoretically, increased anticoagulant effects could be expected when warfarin is combined with coumarin-containing herbs (some plant coumarins exert anticoagulant effects) or with antiplatelet herbs. Conversely, vitamin K-containing herbs can antagonize the effect of warfarin (the action of warfarin is due to its ability to antagonize the cofactor function of vitamin K).

Comprehensive review articles specifically highlighting the mechanisms of herb-to-drug interactions, including evidence of herbs that can modulate CYP or P-glycoprotein have recently been published [9–12].

## Level of Clinical Evidence

In this article, clinical evidence has been categorized into the following levels:

*Level 1:* incomplete case report, presence of other explanatory factors for the adverse reaction, adverse event unlikely from a pharmacological viewpoint.

*Level 2:* case report providing some evidence for an interaction, other causes not fully excluded (e.g. interactions indicated as 'probable' or 'possible' by the Naranjo probability scale).

*Level 3:* well-documented case report; multiple case reports, case series.

*Level 4:* pharmacokinetic trials in patients or healthy volunteers.

*Level 5:* interaction highlighted by case report(s) and confirmed by clinical pharmacokinetic trials.

*Level of evidence 'not applicable':* adverse event highlighted by case report(s) and not confirmed by clinical trials, contradictory data from different clinical trials.

## Clinical Interactions between Herbs and Conventional Drugs

An overview of the clinical data regarding herb-to-drug interactions for a number of herbal remedies known to interact with conventional medicines is reported below.

### *Aloe vera*

*Aloe vera* (Fam. Liliaceae) is used in western countries as a laxative (*A. vera* latex, which contains anthraquinones) and for dermatologic conditions (*A. vera* gel, containing mainly mucilages) [2, 4]. In traditional Chinese

medicine, *A. vera* is mainly employed for inflammatory conditions, diabetes and hyperlipidaemia. Blood loss during surgery as a result of a possible interaction between *A. vera* and the anaesthetic sevoflurane has been reported [13]. An additive effect on platelet function has been hypothesized but not proven since both sevoflurane and *A. vera* ingredients may inhibit platelet aggregation.

Black Cohosh *(Cimicifuga racemosa)*

Black cohosh (*Cimicifuga racemosa* rhizome and roots, Fam. Ranunculaceae), mostly used to treat symptoms of menopause [2, 3], has been associated with serious safety concerns, such as hepatotoxicity, which urgently require further investigation [3, 4].

The effect of black cohosh extract on the activity of human CYP enzymes as well as on P-glycoprotein has been evaluated in a number of clinical trials [14–17] using different probe drugs, including caffeine, midazolam, chlorzoxazone, debrisoquin and digoxin. The results suggest that black cohosh is unlikely to affect the pharmacokinetics of conventional drugs that are metabolized by CYP1A2, CYP3A4, CYP2E1 and CYP2D6 or are substrates of P-glycoprotein. In addition, seven different brands of commercial black cohosh products were found not to affect human CYP using an in vitro liver microsomal technique [18]. On the whole, black cohosh seems to pose only minor risks in patients undergoing conventional pharmacotherapy.

Cat's Claw *(Uncaria tomentosa)*

Cat's claw (*Uncaria tomentosa*, Fam. Rubiaceae) is a medicinal plant from the Amazon rainforest. Due to its immunostimulant and antiviral effects, it has been used for conditions, such as rheumatoid arthritis and AIDS [2]. Cat's claw has been shown to increase the plasma concentration of the protease inhibitors atazanavir, ritonavir and saquinavir [19]. In vitro, cat's claw has been shown to inhibit CYP3A4, which is responsible of the metabolism of the protease inhibitors. However, no human data on the possible modulation of CYP enzymes by cats' claw have been provided to date.

Chamomile *(Matricaria recutita)*

Chamomile, consisting of fresh or dried flower heads of *Matricaria recutita* (Fam. Asteraceae), is used both externally (for skin and mucous membrane inflammations) and internally (for the treatment of gastrointestinal spasms and inflammatory disease of the gastrointestinal tract) [4, 5]. Chamomile contains coumarins, a large class of over 1,300 natural compounds. Some, but definitely not all, coumarin compounds may exert an anticoagulant effect [20]. A case of rectus sheath and retroperitoneal haematomas was reported in a patient under warfarin therapy [21]. It was believed, but not proven, that the coumarin constituents of chamomile may have worked synergistically or additively with warfarin, resulting in over-anticoagulation.

Cranberry *(Vaccinium macrocarpon)*

Cranberry is the American name of the fruit of *Vaccinium macrocarpon* (Fam. Ericaceae); it has been used for decades to prevent urinary tract infections [3, 4], generally in the form of an encapsuled standardized extract, a dilute juice or a dried-juice capsule [4].

On the basis of multiple published cases (including 2 cases of fatal interaction) reporting increased international normalized ratio (INR) and haemorrhage [21–31], serious concerns have been raised regarding a possible interaction with the anticoagulant warfarin. However, these warnings may possibly be attributed to misleading conclusions [32].

With the exception of one study, which showed that capsules containing concentrated cranberry juice increased the area under the INR-time curve of warfarin by 30% [33], a number of clinical trials have consistently shown that cranberry juice, even administered at high doses, did not cause any clinically relevant changes in warfarin pharmacokinetics and pharmacodynamics [34–38]. Clinical evidence indicates the lack of interaction between cranberry juice and some CYP isoenzymes, e.g. CYP2C9, CYP1A2 and CYP3A4 [36–38] necessary for warfarin metabolism [39]. Finally, a clinical trial found that pomelo juice, but not cranberry juice, affected the pharmacokinetics of cyclosporine (CYP3A4 and P-glycoprotein substrate) in humans [40].

Danshen *(Salvia miltiorrhiza)*

Danshen, also known as Chinese salvia or red salvia, are preparations derived from the roots and rhizome of *Salvia miltiorrhiza* (Fam. Lamiaceae). Danshen is widely used in traditional Chinese medicine to prevent and treat cardiovascular conditions, such as acute ischemic stroke and myocardial infarction [2–4]. Danshen can affect haemostasis in several ways, including inhibition of platelet aggregation. Case reports have highlighted the possibility of interactions between warfarin and danshen, resulting in an increased anticoagulant effect [41–44]. A pharmacokinetic mechanism seems unlikely since danshen has been shown to induce intestinal CYP3A4 in 14 healthy volunteers [45].

Dong Quai *(Angelica sinensis)*

*Angelica sinensis* (Fam. Apiaceae), commonly known as 'dong quai', is one of the most popular traditional Chinese medicines [4]. Preparations from its roots are used mainly for dysmenorrhoea, amonorrhoea or excessive menstrual flow. The actions of dong quai are said to be due to the presence of a number of chemical constituents, including coumarins [4], which may have anticoagulant actions [20]. Two well-documented case reports suggest overanticoagulation following co-administration of warfarin and dong quai [46, 47].

Echinacea (*Echinacea* spp.)

Echinacea preparations derive from underground as well as aerial parts of several species of *Echinacea* (Fam. Asteraceae), e.g. *E. angustifolia, E. pallida* and *E. purpurea* [4]. Due to its immunostimulant properties, echinacea is widely used for the prevention and treatment of common infections, such as respiratory tract infections [2–4].

Echinacea seems to pose no serious risk for drug interactions in humans. No verifiable case reports of drug-to-herb interactions with any echinacea product have been published to date. Echinacea did not change the pharmacokinetics of digoxin, a P-glycoprotein substrate [48] nor did it alter the pharmacokinetics of chlorzoxazone (CYP2E1 probe) [17], debrisoquine (CYP2D6 probe) [17, 49], dextromethorphan (CYP2D6 probe) [50] or tolbutamide (CYP2C9 probe) [50]. Some studies have found that echinacea affects caffeine (CYP1A2 probe) and midazolam (CYP3A4 probe) pharmacokinetics; however, this has not been confirmed by other clinical trials [17, 49].

Finally, a recent clinical trial showed that *E. purpurea* root extract did not affect the overall darunavir or ritonavir (a combination of protease inhibitors) pharmacokinetics in HIV patients [51]. Protease inhibitors are mainly metabolized by CYP3A4 and are P-glycoprotein substrates.

Eleuthero *(Eleutherococcus senticosus)*

Eleuthero, also named 'Siberian ginseng', belongs to the same family (Araliaceae) as Asian ginseng *(Panax ginseng)*. Like Asian ginseng, eleuthero is promoted as a 'tonic for invigoration and fortification in times of fatigue and debility or declining capacity for work and concentration, also during convalescence' [5].

Eleuthero, at generally recommended over-the-counter doses, is unlikely to alter the disposition of co-administered medications primarily metabolized by CYP2D6 or CYP3A4 [52].

Increased levels of digoxin have been associated with ingestion of eleuthero [53]. In this case, the patient was asymptomatic for digoxin toxicity despite high plasma levels of the cardiotonic drug. Since eleuthero contains glycosides with structural similarities to digoxin that interfere with digoxin assays, this is not a real clinical herb-to-drug interaction, but rather represents an artefact of digoxin assays.

Garlic *(Allium sativum)*

Garlic (*Allium sativum* L., Fam. Alliaceae) is used in modern phytotherapy to treat hypercholesterolaemia and prevent arteriosclerosis although the clinical evidence is far from compelling [2, 3]. Garlic preparations include garlic powder standardized to contain 1.3% alliin and 0.6% allicin, garlic aged extract, which does not contain allicin but is high in water soluble phytochemicals, such as diallyl sulphides and garlic oil (i.e. essential oil obtained from the distillation of the cloves) [4].

Two garlic preparations, namely garlic oil and garlic powder, have been evaluated for their potential to affect CYP enzymes in clinical trials. The results suggest that garlic oil may selectively inhibit CYP2E1, but not other CYP isoforms (such as CYP1A2, CYP3A4 or CYP2D6) and that garlic powder has no effect on CYP3A4 [54–58]. Recently, it has been shown that a 21-day garlic treatment (aged garlic extract) induces intestinal expression of P-glycoprotein without affecting intestinal or hepatic CYP34A in humans [59].

The most thoroughly studied garlic interactions with conventional drugs include interactions with the anticoagulant warfarin, which, in any case, have not been confirmed by controlled clinical trials or antiretroviral drugs (see details in table 1) [60–67]. Other irrelevant and/or poorly documented interactions include changes in paracetamol pharmacokinetics [68] and hypoglycaemia when combined with the antidiabetic drug chlorpropamide [69].

Ginger *(Zingiber officinale)*

Ginger (rhizome of *Zingiber officinale*, Fam. Zingiberaceae) preparations are effective in attenuating nausea and vomiting during pregnancy and during the post-operative period [2–4]. They showed considerable antiplatelet effects in preclinical studies [4] and this might explain the elevated INR in a patient taking it concomitantly with the anticoagulant phenprocoumon [70]. However, such an interaction has not been confirmed by a clinical trial [71].

Ginkgo *(Ginkgo biloba)*

Extracts from the leaves of the ginkgo tree (*Ginkgo biloba*, Fam. Ginkgoaceae) are used for the treatment of cognitive impairments, dementia, intermittent claudication and tinnitus [2–5]. The effect of ginkgo on various CYP isoforms as well as on P-glycoprotein has been investigated in a number of clinical trials by using different probe drugs, such as alprazolam, midazolam, diazepam, nifedipine (CYP3A4), caffeine (CYP1A2), chlorzoxazone (CYP2E1), debrisoquine (CYP2D6), tolbutamide, diclofenac, flurbiprofen (CYP2C), omeprazole, voriconazole (CYP2C19), fexofenadine, digoxin and talinolol (P-glycoprotein substrates) [55, 56, 72–82]. Given the heterogeneity of the results, firm conclusions cannot be drawn. Nevertheless, the results seem to suggest minor or no effect of ginkgo on the various CYP isoforms or on P-glycoprotein.

It is often mentioned that ginkgo can interact with anticoagulant drugs [2–4]. However, clinical evidence refuted this notion since this herbal product has been shown not to affect blood coagulation or platelet function in humans [83]. Clinical trials have also shown that ginkgo has no additive effect with aspirin on platelet aggregation [84], does not change the antiplatelet activity of clopidogrel and cilostazol [85] and has no effect on warfarin INR and platelet aggregation [71, 86]. In light of these recent controlled clinical data, causality and mechanisms advanced in previous case reports, in which ginkgo was suspected to cause spontaneous hyphaema when associated with aspirin [87], intracerebral haemorrhage when associated with warfarin [88] and intracerebral mass bleeding when associated with ibuprofen [89], should be re-examined.

Finally, single cases suggest that ginkgo may cause priapism when combined with the antipsychotic drug risperidone [90], coma when combined with the atypical antidepressant trazodone [91], fatal seizure when combined with the anticonvulsant drugs valproic acid and phenytoin [92] and virological failure when combined with efavirenz, a non-nucleoside reverse transcriptase inhibitor [93].

It should be noted that, in clinical trials, EGb 761, a well-defined extract of *Ginkgo biloba* leaves, standardized to contain 24% flavone glycosides and 6% terpene lactones, has been used. EGb 761 has generally not been implicated in case reports [83].

Ginseng (Korean Ginseng, *Panax ginseng*)

Preparations of Asian ginseng, obtained from the roots of *Panax ginseng* (Fam. Araliaceae), are used to reduce susceptibility to illness, promote health and longevity, restore male sexual function and aid convalescence [4, 5]. Pure ginsenosides can inhibit platelet aggregation in vitro [4]. However, clinical studies have consistently demonstrated that ginseng extracts have had no significant effect on platelet function in humans [94] and did not change the pharmacokinetics or pharmacodynamics of warfarin [95–97]. Surprisingly, a decreased anticoagulant effect has been reported in a patient taking both ginseng and warfarin [98].

Case reports suggest potentially serious interactions when ginseng is used with the antidepressant phenelzine and the anticancer drug imatinib [99–101] (see table 1 for details). Finally, the clinical results consistently showed that ginseng does not affect CYP enzymes although a slight inhibition of CYP2D6 has been observed [55, 56].

Ginseng (American Ginseng, *Panax quinquefolius*)

*Panax quinquefolius* (Fam. Araliaceae), commonly known as 'American ginseng', is a herbaceous perennial herb native to North America [4, 5]. A clinical study showed that American ginseng reduced the anticoagulant effect of warfarin in healthy volunteers [102] (see table 1 for further details). On the other hand, two clinical trials have recently shown that American ginseng did not affect the pharmacokinetics of the antiretroviral drugs indinavir and zidovudine [103, 104].

Goldenseal *(Hydrastis canadensis)*

Goldenseal (*Hydrastis canadensis,* Fam. Ranunculaceae) has a history of folk medicine use in the treatment of gastrointestinal disturbances, urinary disorders, skin ailments and various infections [2, 4]. A clinical trial showed that goldenseal did not change the disposition of digoxin, suggesting that this herb has no effect on P-glycoprotein [105]. Although one study did not yield the same conclusions [106], convincing clinical evidence suggests that adverse herb-to-drug interactions may result with concomitant ingestion of goldenseal and drugs that are metabolized by CYP3A4 or CYP2D6 [14, 17, 107, 108]. Therefore, although no clinical case report of herb-to-drug interaction has been published to date, goldenseal should be not administered concomitantly with drugs that are metabolized by CYP3A4 or by CYP2D6.

Green Tea *(Camellia sinensis)*

Green tea (*Camellia sinensis* leaves, Fam. Theaceae) is used both as a beverage and as a herbal drug [4]. Possibly due to its vitamin K content, green tea might reduce the anticoagulant effect of warfarin [109]. Furthermore,

green tea has been shown to reduce acid folic and the plasma level of statins through a mechanism that remains to be clarified [110, 111]. Lastly, green tea has minor effects on human CYP3A4 [112, 113].

Kava *(Piper methysticum)*

Preparation from the rhizome and roots of *Piper methysticum* (Fam. Piperaceae) are used for the treatment of anxiety, and the available evidence suggests that kava extracts are superior to placebo for treating patients with anxiety disorders [2–4]. Unfortunately, in the UK and various other European countries, the sale of kava is currently prohibited due to reports of potential hepatotoxicity [4].

In vitro, kavalactones, the active ingredients of kava, have been shown to be potent inhibitors of several enzymes of the CYP450 system [114]. However, clinical trials have shown that, at therapeutic doses, kava inhibits CYP2E1 but not other CYP isoforms, such as CYP3A4, CYP2D6 or CYP1A2. Kava does not affect P-glycoprotein [14, 17, 105, 107, 108].

Some possible pharmacodynamic interactions, highlighted by single case reports have been postulated to occur when combining kava with benzodiazepines, anti-Parkinson or antidepressant drugs (see table 1 for further details) [115–117].

Licorice *(Glycyrrhiza glabra)*

The roots and rhizomes of *Glycyrrhiza glabra* (Fam. Fabaceae) are mainly used for the treatment of peptic ulcer and catarrhs of the upper respiratory tract [2–5]. A preliminary report, published in abstract form only, showed that the ingestion of aqueous licorice extract for 7 days did not significantly alter the pharmacokinetics of midazolam, a CYP3A4 substrate [118]. However, both glycyrrhizin and glycyrrhetic acid (i.e. chemical components of licorice) have recently been shown to induce CYP3A4 in humans [119, 120]. In the absence of definitive data for standardized licorice extracts, it is suggested that this herbal remedy should be used with caution when taken concomitantly with other drugs that interact with CYP3A4.

There is some indirect evidence that licorice may affect the pharmacokinetics of prednisolone. Glycyrrhizin is known to increase the plasma prednisolone concentration in humans and is one of the ingredients of three major traditional Chinese formulations, namely Sho-saiko-To, Saiboku-to, and Sairei-To, which all affected prednisolone pharmacokinetics in healthy volunteers [121, 122].

Milk Thistle *(Silybum marianum)*

Phytotherapeutic milk thistle preparations are obtained from *Silybum marianum* (Fam. Asteraceae) and are used to treat liver diseases [2–4]. *S. marianum* extracts seem to have minor effects on the pharmacokinetics of drugs metabolized by CYP enzymes or transported by P-glycoprotein. With the exception of one study [123], several clinical trials have reliably shown that *S. marianum* extracts did not affect the pharmacokinetics of a number of drugs metabolized by various CYP isoforms (e.g. CYP1A2, CYP2D6, CYP2E1 and CYP3A4) and/or transported by P-glycoprotein [15, 16, 124–130]. Overall, milk thistle seems to pose no risk for drug interactions in humans.

Peppermint *(Mentha piperita)*

Peppermint leaf and oil from *Mentha piperita* (Fam. Labiateae) have a long history of use in digestive disorders [3, 4]. Recent evidence suggests that enteric-coated peppermint oil may be effective in relieving some of the symptoms of irritable bowel syndrome [3]. Some clinical data suggest that peppermint might increase the levels of drugs metabolized by CYP3A4, such as felodipine [131].

Red Yeast Rice

Red yeast rice is produced by fermentation of washed and cooked rice using the fungus *Monascus purpureus* and is used to lower blood cholesterol [3, 4]. Red yeast rice has been suspected to cause rhabdomyolysis in a a stable renal-transplant patient under cyclosporine treatment [132] (see table 1 for further details). It should be noted that red yeast rice may cause myopathy even when administered alone [133].

Saw Palmetto *(Serenoa repens)*

*Serenoa repens* (Fam. Arecaceae) preparations are well tolerated by most users and are not associated with serious adverse events [2–4]. No evidence for drug interactions with saw palmetto has been published. Two clinical studies demonstrated that saw palmetto had no significant effect on CYP1A2, CYP2D6, CYP2E1 or CYP3A4 in healthy volunteers [50, 134]. Extracts from *S. repens* berries are the most widely used herbal preparations for the treatment of benign prostatic hyperplasia [2–5, 200]. Saw palmetto, pumpkin and vitamin E are ingredients of curbicin, a herbal formulation used to relieve symptoms associated with benign prostatic hyperplasia. Two cases of increased INR were reported after co-administration of curbicin and warfarin [135]; the INR normalized after discontinuation of curbicin. No anticoagulant effect has

been found in the literature associated with both saw palmetto and pumpkin. However, vitamin E has been shown to antagonize the effect of vitamin K and may lead to an increased risk of bleeding, particularly in patients taking oral anticoagulants [136]. The currently available evidence suggests that saw palmetto is unlikely to pose serious health threats to patients combining it with conventional drugs.

*Schisandra chinensis*

*Schisandra chinensis* (Wuweizi, Fam. Schizandraceae) is used in modern Chinese medicine as an adaptogenic drug [137]. A clinical trial showed that the herb increased the area under the curve and $T_{max}$ of tanilolol, a P-glycoprotein substrate [82]. Thus, patients receiving *S. chinensis* might require dose adjustments when treated with drugs primarily transported by P-glycoprotein.

*Schisandra sphenanthera*

*Schisandra sphenanthera* (Nan-Wuweizi) is widely used to treat viral and drug-induced hepatitis in China [137]. Two clinical trials showed that extracts obtained from *S. sphenanthera* increased the oral bioavailability of the immunosuppressive drug tacrolimus, which is metabolized by CYP3A4 and P-glycoprotein [138, 139]. A further study showed that *S. sphenanthera* increased the oral bioavailability of midazolam (CYP3A4 substrate) [140]. Overall, *S. sphenanthera* preparations should not be co-administered with CYP3A4-metabolized drugs.

Soy *(Glycine max)*

Soy beans, obtained from *Glycine max* (Fam. Fabaceae), are very rich in phytoestrogens, i.e. non-steroidal plant-derived compounds possessing a weak oestrogenic activity. Soy phyto-oestrogens are claimed to exert beneficial effects in the treatment of menopausal symptoms and prevention of heart disease and cancer [2, 4]. Decreased INR has been reported in a patient under warfarin therapy [141]. On the other hand, a clinical study showed that a 14-day treatment with soy extract did not significantly influence the pharmacokinetics of losartan and its active metabolite E-3174 in 18 healthy Chinese female volunteers [142].

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

*Hypericum perforatum* L. (St. John's wort) extracts are widely used as a safe alternative to conventional antidepressant drugs for mild to moderate forms of depressive disorders [2, 5]. The herb contains numerous compounds with documented biological activity, including the naphthodianthrone hypericin, a broad range of flavonoids, and the phloroglucinol hyperforin, which inhibits the re-uptake of several brain neurotransmitters, including 5-hydroxytryptamine (5-HT, serotonin) [4].

The possible interactions with conventional medicines are the most important risk associated with the intake of *H. perforatum* extracts [143]. St. John's wort represents the herbal product that is most involved in herb-to-drug interactions. Clinical evidence suggests that St. John's wort may cause both pharmacokinetic and pharmacodynamic interactions. Using well-established probe drugs, a great number of clinical trials have consistently shown that St. John's wort induced P-glycoprotein as well as CYP3A4, CYP2E1 and CYP2C19, with no effect on CYP1A2, CYP2D6 or CYP2C9 [144–157]. Induction of CYP enzymes and P-glycoprotein is caused by hyperforin via activation of the pregnane X receptor [158–161].

Pharmacodynamic interactions may occur when St. John's wort is given together with drugs that enhance 5-HT signaling in the brain (e.g. 5-HT re-uptake inhibitors, 5-HT ligands). St. John's wort has been shown to clinically interact with a number of conventional drugs mostly via these pharmacokinetic and/or pharmacodynamic mechanisms; such interactions take place with immunosuppressants (cyclosporine, tacrolimus, prednisone), hormones (oral pill, tibolone), cardiovascular drugs (the anticoagulants warfarin and phenprocoumon, the cardiac inotropic drug digoxin, the antilipidaemic drugs simvastatin, rosuvastatin and atorvastatin, the calcium blockers nifedipine and verapamil, the $\beta_1$-adrenoreceptor blocker talinolol, the anti-anginal drug ivabradine), antiretroviral drugs (indinavir, nevirapine), anticancer drugs (irinotecan, imatinib), drugs acting on the CNS (anaesthetics, the anxyolityc drugs alprazolam, midazolam, quazepam and buspirone, the antidepressants sertraline, nefazodone, paroxetine, venlafaxine and amitriptyline, the anti-epileptic drugs mephenytoin, drugs for addicted patients, such as methadone and bupropion, the centrally acting muscle relaxant chlorzoxazone, the antitussive drug dextromethorphan), anti-ulcer medications (omeprazole), antidiarrhoeal drugs (loperamide), drugs acting on the respiratory system (theophylline, fexofenadine), antifungal drugs (voriconazole) and antimigraine medicines (eletriptan) [55, 56, 143, 146–151, 154, 162–221] (see table 1 for further details).

Well-documented and clinically relevant interactions include: (1) reduced blood cyclosporine concentration associated in some cases to rejection episodes; (2) reduced efficacy of the oral pill, resulting in unwanted pregnancy; (3) reduced plasma concentration of antiretroviral (e.g.

indinavir, nevirapine) and anticancer drugs (e.g. imatinib, irinotecan).

Valerian *(Valeriana officinalis)*

Valerian (*Valeriana officinalis*, Fam. Valeraniaceae) root preparations are widely available in a variety of commercial preparations as a sleep aid. Clinical evidence supports the notion that valerian is a safe herb associated with only rare adverse events [2–4]. Valerian has no impact on a number of CYP isoenzymes, including CYP3A4, CYP2D6, CYP2E1, CYP1A2 [14].

Valerian might theoretically potentiate the effect of CNS depressants. Hand tremor, dizziness, throbbing and muscular fatigue have been reported in a patient self-medicated with valerian and passion flower *(Passiflora incarnata)* while on lorazepam treatment. Also, a brief episode of acute delirium has been reported in a patient taking the antidiarrhoeal drug loperamide in combination with St. John's wort and valerian [223].

### Other Herbs Involved in Drug Interactions

Other herbal products that have been implicated in drug interactions include betel nut (*Areca catechu*, used for the preparation of a relaxing/refreshing beverage) [224], chlorella *(Chlorella pyrenoidosa)*, a unicellular fresh water green alga used mainly as a potential source of food and energy and also believed to have some therapeutic benefits [225], boldo *(Peumus boldus)* used as a choleretic/cholagogue drug [226], fenugreek *(Trigonella foenum-graecum)*, mostly used for the treatment of hypercholesterolaemia and diabetes mellitus [226], evening primrose oil *(Oenothera biennis)*, mostly used in dermatology as well as for the treatment of rheumatoid arthritis [227], maitake *(Grifolia frondosa)*, an edible mushroom with potential anticancer benefits [228], mistletoe *(Viscum album)* used as a palliative therapy for malignant tumors [229], prickly pear cactus *(Opuntia polyacantha)*, traditionally used in Mexico for the treatment of diabetes [230], goji *(Lycium barbarum)*, used in traditional Chinese medicine in cases of loss of energy, diabetes and liver disorders) [231, 232], and hibiscus *(Hybiscus sabdariffa)*, used in folk medicine for the treatment of hypertension [233, 234]. Details of such interactions are reported in table 1.

Gums, mucilages, pectins or fibers contained in several medicinal plants have the ability to bind, trap and form viscous matrices with concurrently administered drugs. Hence, they may reduce their absorption. For example, a decrease in the absorption of lovastatin (associated to increased LDL levels) was observed in patients who took the statin concomitantly with pectin or oat bran [235]. Clinical data have shown that plant products, such as gum guar (from *Cyamopsis tetragonolobus*), acacia gum (from *Acacia senegal*), or guggulipid (a standardized neutral fraction extract of gum guggul, an oleoresin obtained from *Commiphora mukul*) may reduce the absorption of drugs, such as metformin [236], amoxicillin [237], propranolol [238], and digoxin [239]. A case of a decreased INR, suggestive of decreased anticoagulant effect, has been reported in a 57-year old man who began treating himself with an aqueous extract of the boiled roots of *Commiphora molmol* with his usual warfarin [240]. *C. molmol,* one of the primary trees used in the production of myrrh, is traditionally used for the treatment of diabetes mellitus.

Finally, clinical studies have shown that hawthorn *(Crategus oxyacantha)*, used for the treatment of congestive heart failure), had no effect on the pharmacokinetics of digoxin (P-glycoprotein substrate) [241] and *Citrus aurantium* subspecies *amara* (bitter orange peel) used for dyspeptic ailments, had no effect on various CYP isoforms, namely CYP3A4, CYP1A2, CYP2E1, and CYP2D6 [49].

### Patient Characteristics

Characteristics of the patient, such as age, frailty, infrequent genotypes, ethnicity, gender, and comorbidity [242] should be taken into account when considering herb-to-drug interactions.

It is well known that polymorphisms in the genes for drug-metabolizing enzymes or transporters may influence herb-to-drug interactions [12]. For example, ginkgo can induce omeprazole hydroxylation in a CYP2C19 genotype-dependent manner (i.e. the effect has been shown to be more pronounced in poor metabolizers than in extensive metabolizers) [79]. Wang et al. [147] also found that St. John's wort increased CYP2C19 activity, as revealed by the increased urinary 4′-hydroxymephenytoin excretion in CYP2C19 wild-genotype subjects, but not in CYP2C19 poor metabolizers. Conversely, another clinical trial found that St. John's wort increased the clearance of fexofenadine (P-glycoprotein substrate) and midazolam (CYP3A4 substrate) in six ethnic groups (i.e. Caucasian, African American, Hispanic, Chinese, Indian and Malawy) and there was no significant difference in the extent of induction between the ethnic groups [151].

**Table 1.** Clinical interactions between herbal medicines and prescribed drugs

| Herbal medicine (common and Latin name) | Prescribed drug | Clinical result of interaction | Source of evidence Level of evidence (levels 1–5)[1] | Comment |
|---|---|---|---|---|
| Aloe *Aloe vera* | Sevoflurane | Blood loss | One case report [13] Level of evidence: 2 | The report described a 35-year-old woman who lost 5 l of blood during surgery as a result of a possible interaction between *A. vera* and the anaesthetic drug sevoflurane. The patient took *A. vera* (preparation not specified) for leg pain for the last 2 weeks before general anaesthesia. The adverse event was believed to be possible. An additive effect on platelet function has been postulated, but not demonstrated. |
| Betel nut *Arecha catechu* | Procyclidine | Rigidity, bradykinesia, jaw tremors | One case report [224] Level of evidence: 3 | A pharmacodynamic mechanism is likely to be involved (antagonistic action of arecoline from betel nut to the anticholinergic agent procyclidine). The report was well documented and appeared to provide reliable evidence. |
| Boldo *Peumus boldus* | Warfarin | Increased anticoagulant effect | One case report [226] Level of evidence: 2 | The patient also took fenugreek. Both boldo and fenugreek contain coumarins, which might exert an anticoagulant action. The Naranjo probability scale suggests a probable association between boldo and fenugreek and increased bleeding time in patients treated with warfarin. |
| Cat's claw *Uncaria tomentosa* | Protease inhibitors (atazanavir, ritonavir and saquinavir) | Increased blood concentration of the protease inhibitors | One case report [19] Level of evidence: 2 | The increase in the serum trough concentration of the protease inhibitors atazanavir, ritonavir and saquinavir was observed in a 45-year-old HIV-positive woman. The Horn drug interaction probability scale indicated the interaction as possible. The mechanism needs to be determined. |
| Chamomile *Matricaria recutita* | Warfarin | Bleeding | One case report [21] Level of evidence: 2 | Rectus sheath and retroperitoneal haematomas were reported in a 70-year-old woman under warfarin therapy [44]. The patient disclosed the use of a chamomile-based skin lotion to alleviate her pedal oedema and the use of 4–5 cups per day of chamomile tea to relieve her sore throat. Chamomile contains coumarins, which might exert an anticoagulant action. |
| Chlorella *Chlorella pyrenoidosa* | Warfarin | Decreased anticoagulant effect | One case report [225] Level of evidence: 2 | Chlorella is one of the vitamin K-rich foods. Thus, it may inhibit the anticoagulant effect of warfarin. |
| Cranberry *Vaccinium macrocarpon* | Warfarin | Increased anticoagulant response, including fatal haemorrhage | Multiple case reports [21–31] Level of evidence: not applicable | Two of such reports described cases of fatal interaction. This interaction has not been confirmed by clinical trials [34–38, 40]. Nevertheless, due to the existence of different cranberry preparations, patients taking warfarin with cranberry products should be cautiously monitored for INR changes and possible bleeding. |
| Danshen *Salvia milthiorriza* | Midazolam | Increased midazolam blood concentration | One pharmacokinetic trial [45] Level of evidence: 4 | Danshen may induce intestinal CYP3A4. Caution should be taken when danshen products are used in combination with therapeutic drugs metabolized by CYP3A4. |
| | Warfarin | Increased anticoagulant effect | Three case reports [41–44] Level of evidence: 3 | An additive effect on coagulation could explain such an interaction. |
| Don quai *Angelica sinensis* | Warfarin | Increased anticoagulant effect | Two case reports [46, 47] Level of evidence: 3 | The reports were well documented. Dong quai contains coumarins, which might exert an anticoagulant action. |
| Echinacea *Echinacea* spp. | Caffeine | Possible reduction in caffeine blood concentration | One pharmacokinetic trial [49] Level of evidence: not applicable | Caffeine and midazolam are CYP2A1 and CYP3A4 probes, respectively. These results have not been confirmed by other trials. Comparisons between such studies are difficult because different species of Echinacea, different parts of the plant and different preparations have been used. |
| | Midazolam | Possible increased oral bioavailability of midazolam (CYP3A substrate) | One pharmacokinetic trial [50] Level of evidence: not applicable | |

**Table 1** (continued)

| Herbal medicine (common and Latin name) | Prescribed drug | Clinical result of interaction | Source of evidence Level of evidence (levels 1–5)[1] | Comment |
|---|---|---|---|---|
| Evening primrose *Oenothera biennis* | Fluphenazine | Seizures | Two cases in a clinical trial [227] Level of evidence: 3 | Gamalenic acid from evening primrose oil may lower the seizure threshold. |
| Fenugreek *Trigonella foenum-graecum* | Warfarin | Increased anticoagulant effect | One case report [226] Level of evidence: 2 | The patient also took boldo. Both boldo and fenugreek contain coumarins, which might exert an anticoagulant action. The Naranjo probability scale suggests a probable association between boldo and fenugreek and increased bleeding times in patients treated with warfarin. |
| Garlic *Allium sativum* | Chlorzoxazone | Decreased serum 6-hydroxychlorzoxazone/ chlorzoxazone ratios | Two pharmacokinetic trials [55, 56] Level of evidence: 4 | Inhibition of CYP2E1 by garlic can explain such an interaction. |
| | Chlorpropamide | Hypoglycaemia | One case report [69] Level of evidence: 1 | The patients also took karela, which might have caused the interaction. |
| | Fluindione | Decreased fluindione anticoagulant effect | One case report [63] Level of evidence: 1 | The interaction needs to be confirmed. The mechanism is unknown. |
| | Paracetamol | Changes in paracetamol pharmacokinetic variables | One pharmacokinetic trial [68] Level of evidence: 4 | Garlic (daily doses of aged garlic extract equivalent to 6–7 cloves of garlic daily for 3 months) changed the pharmacokinetics of paracetamol in in 16 volunteers. This interaction has probably no clinical significance. |
| | Ritonavir | Severe gastrointestinal toxicity | One case report [67] Level of evidence: 1 | The interaction needs to be confirmed. The mechanism is unknown. A clinical trial showed no effect of garlic on ritonavir pharmacokinetics [66]. |
| | Saquinavir | Decreased saquinavir blood concentration | One pharmacokinetic trial [64] Level of evidence: 4 | A significant decrease (about 50%) in the plasma concentration of the protease inhibitor saquinavir was observed in 10 healthy volunteers after administration of garlic (Garlipure®, 2 capsules/day) for 3 weeks. Garlic possibly induces P-glycoprotein in the gut, thus reducing saquinavir absorption. |
| | Warfarin | Increased anticoagulant effect | Two cases in one publication [60] Level of evidence: not applicable | Such an interaction has not been confirmed in clinical trials [61, 62]. |
| Ginger *Zingiber officinale* | Phenprocoumon | Increased anticoagulant effect | One case report [70] Level of evidence: not applicable | The interaction resulted in an elevated INR (up to 10) and epistaxis in a 76-year-old woman under long-term phenprocoumon therapy (phenprocoumon is a warfarin analogue). The INR returned to the normal range after ginger was stopped and vitamin K1 given. Ginger preparations have shown considerable antiplatelet effects in preclinical studies. However, a clinical trial showed that ginger did not modify the pharmacokinetics and pharmacodynamics of warfarin (phenprocoumon is a warfarin analogue) [71]. |
| Ginkgo *Ginkgo biloba* | Anticonvulsivant (valproic acid and phenytoin) | Fatal seizure | One case report [92] Level of evidence: 1 | The case was a 55-year-old male patient [92]. A fatal seizure occurred and autopsy revealed subtherapeutic serum levels of both the anticonvulsants. The interaction needs to be confirmed. |
| | Antiplatelet/ anticoagulant drugs/NSAIDs | Spontaneous hyphaema (aspirin), fatal intracerebral haemorrhage (ibuprofen), intracerebral haemorrhage (warfarin) | Single case reports [87–89] Level of evidence: not applicable | Clinical trials have consistently shown that ginkgo had no additive effect with aspirin on platelet aggregation [84], did not change the antiplatelet activity of clopidogrel and cilostazol [85] and had no effect on warfarin INR and platelet aggregation [71, 86]. |

**Table 1** (continued)

| Herbal medicine (common and Latin name) | Prescribed drug | Clinical result of interaction | Source of evidence Level of evidence (levels 1–5)[1] | Comment |
|---|---|---|---|---|
| Ginkgo *Ginkgo biloba* | Efavirenz | Virologic failure associated to decreased efavirenz blood concentration | One case report [93] Level of evidence: 2 | Virological failure was described in a 47-year-old HIV-infected patient who was under antiretroviral therapy with efavirenz, a non-nucleoside reverse transcriptase inhibitor. During the past 10 years, he had always been very compliant. The patient revealed the use of ginkgo (preparation not reported in the original article) for a few months. No other comedication was used or discontinued in this time frame. Biological assays revealed decreased efavirenz concentration, coinciding with an increase in viral load. The mechanism needs to be elucidated. |
| | Omeprazole | Reduction in blood concentrations of omeprazole and omeprazole sulphone | One pharmacokinetic trial [79] Level of evidence: 4 | Omeprazole is a CYP2C19 probe. However, another trial showed that ginkgo did not affect the pharmacokinetics of voriconazole, another CYP2C19 probe. |
| | Risperidone | Priapism | One case report [90] Level of evidence: 2 | Priapism, lasting for 4 h, was reported in a 26-year-old man [90]. In rare instances, priapism can be a serious adverse effect of antipsychotic medications. The interaction needs to be confirmed. The mechanism is unknown. Both ginkgo and risperidone have vessel-dilating properties. |
| | Tolbutamide | Possible decreased tolbutamide blood concentration | One pharmacokinetic trial [77] Level of evidence: 4 | This interaction was not confirmed by another clinical trial. Tolbutamide is a CYP2C9 substrate. The clinical significance of such an interaction is uncertain. |
| | Trazodone | Coma | One case report [91] Level of evidence: 2 | The patient described was an 80-year-old woman with Alzheimer's disease who fell into a coma after taking a low dose of the atypical antidepressant trazodone with ginkgo [91]. The interaction needs to be confirmed. The mechanism is unknown. The report provides some evidence for an interaction, but the event may be due to other causes. |
| | Talinolol | Increased talinolol blood concentration | Two pharmacokinetic trials by the same research group [81, 82] Level of evidence: 4 | Talinolol is a P-glycoprotein substrate. However, other trials have shown that ginkgo did not affect the pharmacokinetics of other P-glycoprotein probes, such as digoxin and fexofenadine. |
| Ginseng (Korean ginseng) *Panax ginseng* | Imatinib | Hepatotoxicity | One case report [101] Level of evidence: 2 | The adverse event was described in a 26-year old man with chronic myelogenous leukaemia [101]. The patient's only lifestyle modification prior to the diagnosis of hepatotoxicity was daily ingestion of *P. ginseng* via energetic drinks for the past 3 months. Both imatinib and ginseng were discontinued. Imatinib was later restarted at the same dose with no recurrent elevations in his liver enzyme levels. The Horn drug interaction probability scale indicated the interaction was probable. The mechanism of such an interaction is not known. |
| | Phenelzine | Sleeplessness, tremor and headaches | Two published cases in a single subject [99, 100] Level of evidence: 3 | The report described a 64-year-old depressed woman who experienced insomnia, headache and mania when she combined ginseng (preparation and dose not reported) with the antidepressant phenelzine. Three years later, after involuntary re-challenge, the patient again experienced similar symptoms. These 2 case reports were published in the late 1980s. Since then, no other case of interaction between phenelzine and ginseng has been reported. |
| | Warfarin | Reduced anticoagulant effect | One case report [98] Level of evidence: not applicable | This is a surprising interaction because ginsenosides can inhibit platelet aggregation in vitro. In addition, clinical studies have consistently demonstrated that ginseng extracts have no significant effect on platelet functions in humans and do not change the pharmacokinetics or pharmacodynamics of warfarin [95–97]. |

**Table 1** (continued)

| Herbal medicine (common and Latin name) | Prescribed drug | Clinical result of interaction | Source of evidence Level of evidence (levels 1–5)[1] | Comment |
|---|---|---|---|---|
| Ginseng (American ginseng) *Panax quinquefolius* | Warfarin | Reduced warfarin blood concentration and anticoagulant effect | Clinical trial [102] Level of evidence: 4 | The herb (1 g/daily) reduced the peak INR, $C_{max}$, and warfarin AUC after 2 weeks' treatment in 20 healthy volunteers (randomized, double-blind, placebo-controlled trial). A limitation of the study is that the sample consisted of young healthy volunteers rather than patients taking therapeutic doses of warfarin. The mechanism of such an interaction needs to be investigated. If we assume that American ginseng inhibits platelet aggregation in vivo (ginsensosides are known to inhibit platelet aggregation), an increase – rather than a decrease – of the INR should be expected. |
| Goji (Chinese wolfberry) *Lycium barbarum* | Warfarin | Increased anticoagulant effect | Two case reports [231, 232] Level of evidence: 3 | In one case, re-challenge confirmed such interaction. The mechanisms is unknown. |
| Goldenseal *Hydrastis canadensis* | Debrisoquine | Decreased debrisoquine urinary recovery ratio | One pharmacokinetic trial [108] Level of evidence: 4 | This interaction is suggestive of CYP2D6 inhibition. |
| | Midazolam | Increased midazolam blood concentration | One pharmacokinetic trial [14] Level of evidence: 4 | This interaction is suggestive of CYP3A4 inhibition. However, goldenseal did not change the pharmacokinetics of indinavir, another CYP3A4 substrate. |
| Green tea *Camellia sinensis* | Folic acid | Decreased folate blood concentration | One pharmacokinetic trial [110] Level of evidence: 4 | Folic acid is a water-soluble vitamin which plays a role in the prevention of neural tube defects. This open-label, randomized cross-over trial showed that both green and black tea reduced folate $C_{max}$ and the AUC. The herbal preparations were standardized in their epigallocatechin, gallocatenin and epicatechin contents and administered as infusions (250 ml of tea, twice daily; the concentration of the tea drinks was 0.3 g/250 ml). |
| | Simvastatin | Statin intolerance associated with increased simvastatin blood levels | One case report [111] Level of evidence: 2 | The event was reported in a 61-year-old man with a history of primary hypercholesterolaemia. Treatment with different statins was unsuccessful because of early muscle intolerance. After obtaining the patient's informed consent, simvastatin bioavailability during usual green tea consumption was assessed. The results showed an increased plasma concentration of simvastatin lactone and simvastatin acid after consumption of green tea, suggesting an evident interaction between green tea and simvastatin. The mechanism of such an interaction is unknown. Green tea has minor effects on CYP3A4, the main simvastatin-metabolizing enzyme [112, 113]. |
| | Warfarin | Decreased anticoagulant effect | One case report [109] Level of evidence: 2 | The report described a 44-year-old man whose INR decreased from approximately 3.8 to 1.4. The decreased INR was believed to be due to green tea, which the patient had consumed, as a beverage, at the dose of approximately 2–4 l per day for about 1 week [161]. Green tea contains high amounts of vitamin K, which may antagonize the effect of warfarin. |
| Hibiscus *Hibiscus sabdariffa* | Chloroquine | Reduced blood concentration of chloroquine | One pharmacokinetic trial [233] Level of evidence: 4 | The possible interaction between hibiscus and chloroquine, a drug used in the treatment or prevention of malaria, was examined following oral co-administration of the synthetic drug with three common Sudanese beverages, i.e. aradaib *(Tamarindus indica)*, hibiscus and lemon *(Citrus limetta)*, in healthy males. Each of the three beverages significantly reduced the AUC and $C_{max}$ of chloroquine. A parallel reduction in the drug's anti-malarial efficacy might be expected. The mechanism is presently unknown. |

**Table 1** (continued)

| Herbal medicine (common and Latin name) | Prescribed drug | Clinical result of interaction | Source of evidence Level of evidence (levels 1–5)[1] | Comment |
|---|---|---|---|---|
| Hibiscus *Hibiscus sabdariffa* | Paracetamol | Changes in some pharmacokinetic parameters of acetaminophen | One pharmacokinetic trial [234] Level of evidence: 4 | Zobo drink, a sweetened water extract of the dried calyx of *H. sabdariffa*, altered some pharmacokinetic parameters of the antipyretic-analgesic drug paracetamol (acetaminophen) in 6 healthy volunteers. The clinical significance of such an interaction is uncertain. |
| Kava *Piper methysticum* | Alprazolam | Lethargic and disoriented state | One case report [115] Level of evidence: 1 | The adverse event was observed in a 54-year-old woman who took this herb in combination with the benzodiazepine alprazolam. Although an additive effect on GABA receptors could explain this interaction, the report contained inadequate information to assess the likelihood of the interaction. |
| | Chlorzoxazone | Decreased 6-hydroxychlorzoxazone/ chlorzoxazone serum ratios | One pharmacokinetic trial [14] Level of evidence: 4 | Chlorzoxazone is a CYP2E1 probe. Kava should not be taken concomitantly with CYP2E1 substrates. |
| | Levodopa | Reduced efficacy | One case report [116] Level of evidence: 2 | The reduced activity of levodopa (a precursor of dopamine) was observed in a 76-year-old Parkinson's disease patient. A dopamine antagonism could explain this interaction, which, in any case, should be confirmed. |
| | Paroxetine | Lethargic state | One case report [117] Level of evidence: 2 | The adverse event was described in a 44-year-old male who took a herbal combination containing valerian and kava in combination with the antidepressant drug paroxetine. The interaction needs to be confirmed. The mechanism is unknown. |
| Maitake *Grifolia frondosa* | Warfarin | Increased anticoagulant effect | One case report [228] Level of evidence: 2 | The Horn drug interaction probability scale indicated the interaction was possible. The mechanism is unknown. |
| Milk thistle *Silybum marianum* | Metronidazole | Decreased metronidazole blood concentration | One pharmacokinetic trial [123] Level of evidence: 4 | Metronidazole is a P-glycoprotein substrate and is also metabolized by CYP3A4 and CYP2C9. With the exception of one study, showing that silymarin (140 mg/daily for 7 days) decreased the serum concentration and AUC of metronidazole [123], several clinical trials have reliably shown that that *S. marianum* extracts did not affect the pharmacokinetics of a number of drugs which are metabolized by various CYP isoforms (e.g. CYP1A2, CYP2D6, CYP2E1 and CYP3A4) and/or transported by P-glycoprotein. These include indinavir, irinotecan, caffeine, midazolam, nifedipine, ranitidine, rosuvastatin, chlorzoxazone and debrisoquine [15, 16, 124–130]. |
| Mistletoe *Viscum album* | Busulphan | Organ fibrosis and death | One case report [229] Level of evidence: 1 | The mechanism is unclear. |
| Passion flower *Passiflora incarnata* | Lorazepam | Hand tremor, dizziness, throbbing and muscular fatigue | One case report [222] Level of evidence: 2 | The patients also took valerian. Both valerian and passion flower may exert an additive CNS-depressant effect with the benzodiazepine lorazepam. |
| Peppermint *Mentha piperita* | Felopidine | Increased felopidine blood concentration | Pharmacokinetic trial [131] Level of evidence: 4 | Peppermint oil increased the AUC and $C_{max}$ of both felodipine and its metabolite dehydrofelodipine. Peppermint oil and its active ingredients, menthol and menthyl acetate, were found to be moderately potent reversible inhibitors of CYP3A4 activity in vitro. Thus, the interaction likely occurs via CYP3A4 inhibition. |
| Prickly pear cactus *Opuntia polyacantha* | Glipizide and metformin | Hypoglycaemic effect | One case report [230] Level of evidence: 2 | The Naranjo probability scale suggests the adverse event to be probable. An additive hypoglycaemic effect could explain such an interaction (prickly pear cactus reduces blood glucose levels in patients with type 2 diabetes mellitus). |

**Table 1** (continued)

| Herbal medicine (common and Latin name) | Prescribed drug | Clinical result of interaction | Source of evidence Level of evidence (levels 1–5)[1] | Comment |
|---|---|---|---|---|
| Red yeast rice[2] | Cyclosporine | Rhabdomyolysis | One case report [132] Level of evidence: 2 | The adverse event was observed in a stable renal transplant recipient under cyclosporine treatment – a 58-year old woman – and was attributed to a mixture of herbal products containing red yeast rice. The adverse event resolved when the intake of the herbal product stopped. Red yeast rice contains natural statins (CYP3A4 substrates) whose blood concentration might be theoretically increased by cyclosporine (inhibitor of CYP3A4). If confirmed, this represents an usual interaction in which a conventional drug (i.e. cyclosporine) increases the toxicity of a herbal product (i.e. red yeast rice). |
| *Schisandra chinesis* | Talinolol | Increased talinolol blood concentration | One pharmacokinetic trial [82] Level of evidence: 4 | *S. chinensis* extract significantly increased both the tanilolol AUC (47% increase) and $T_{max}$ (51% increase), suggesting that the herbal extract inhibited P-glycoprotein in humans. |
| *Schisandra sphenanthera* | Tacrolimus | Increased tacrolimus blood concentration | Two pharmacokinetic trials [138, 139] Level of evidence: 4 | *S. sphenanthera* and tacrolimus are often co-administered when treating renal and liver transplant recipients in China. *S. sphenanthera* is a CYP3A4 inhibitor. *S. sphenanthera* preparations should not be co-administered with CYP3A4-metabolized drugs, including tacrolimus. |
| | Midazolam | Increased midazolam blood concentration | One pharmacokinetic trial [140] Level of evidence: 4 | *S. sphenanthera* (3 capsules daily for 7 days, each capsule containing 11.25 mg deoxyschizandrin) increased the oral bioavailability of midazolam (a CYP3A4 probe) in 12 male volunteers. |
| Soy *Glycine max* | Warfarin | Decreased anticoagulant effect | One case report [141] Level of evidence: 2 | The adverse event was reported in a 70-year-old white man who developed subtherapeutic INR values after ingesting soy protein in the form of soy milk. An objective causality assessment of this case revealed that the INR decline was in the range of possible to probable. The mechanism of such an interaction is unknown. |
| St. John's wort *Hypericum perforatum* | Adrenergic vasopressors (ephedrine, phenylephrine) | Decreased responsiveness to vasopressors | One case report [212] Level of evidence: 2 | The interaction needs to be confirmed. The mechanism is unknown. |
| | Alprazolam | Decreased alprazolam blood concentration | One pharmacokinetic trial [144] Level of evidence: 4 | Alprazolam is a CYP3 probe. No effect of St. John's wort on CYP3A4 after short-time St. John's wort administration (i.e. 3 days) or with St. John's wort extracts with low hyperforin content. |
| | Amitriptyline | Decreased amitriptyline blood concentration | One pharmacokinetic trial [210] Level of evidence: 4 | The interaction likely occurs via induction of CYP3A4 and/or induction of P-glycoprotein. The therapeutic manifestation of such an interaction has not been determined to date. Perhaps surprisingly, St. John's wort (extract standardized to 0.3% hypericin, 300 mg 3 times daily for 14 days) did not change the carbamazepine pharmacokinetics in 8 volunteers (5 males and 3 females) [214]. The lack of interaction can be explained considering the fact that carbamazepine is metabolized not only by CYP3A4 but also by other CYP isoforms, such as CYP2C8 [215]. |
| | Anaesthetics | Delayed emergence | Two case reports [211, 212] Level of evidence: 2 | Delayed emergence and cardiovascular collapse [212] have been reported in young women during general anaesthesia. In one case [211] anaesthesia was induced by fentanyl and propofol and maintained with sevoflurane in oxygen and nitrous oxide; in the other case [212], anaesthesia was induced with fentanyl and propofol, with tubocurarine and succinylcholine used as muscle relaxants. The American Society of Anaesthesiologists advises that the use of St. John's wort be discontinued 2 or 3 weeks before surgery. |

**Table 1** (continued)

| Herbal medicine (common and Latin name) | Prescribed drug | Clinical result of interaction | Source of evidence Level of evidence (levels 1–5)[1] | Comment |
|---|---|---|---|---|
| St. John's wort *Hypericum perforatum* | Atorvastatin | Reduced efficacy of atorvastatin | One pharmacokinetic trial [193] Level of evidence: 4 | The interaction likely occurs via induction of CYP3A4 and/or induction of P-glycoprotein. |
| | Bupropion | Orofacial dystonia | One case report [217] Level of evidence: 2 | The case of prolonged orofacial dystonia was reported in a 58-year-old female. The patient presented dystonic movements affecting the right side of her face, neck and right arm. Both bupropion and St. John's wort are known to inhibit the re-uptake of dopamine, potentially resulting in additive effects on dopaminergic transmission and hence in dopaminergic side effects such dystonia. |
| | | Decreased bupropion blood concentration | One pharmacokinetic trial [218] Level of evidence: 4 | A pharmacokinetic mechanism has been postulated. |
| | Buspirone | Hypomanic episode, serotonin syndrome | One case report [205] Level of evidence: 2 | The adverse event was reported in a 27-year-old female. A pharmacodynamic mechanism has been postulated (additive effect on 5-HT reuptake). |
| | Chlorzoxazone | Increase in hydroxylchlorzoxazone/chlorzoxazone serum ratio | Two pharmacokinetic trials [55, 56] Level of evidence: 4 | The two clinical trials found that St. John's wort (extract standardized to 0.3% hypericin, 300 mg 3 times daily for 28 days) increased the hydroxychlorzoxazone/chlorzoxazone serum ratios, suggesting CYP2E1 induction. Interestingly, the effect was found to be more pronounced in young than in elderly subjects. |
| | Cyclosporine | Decreased blood concentration of cyclosporine | Multiple case reports, case series and two clinical trials [149, 158, 162–176] Level of evidence: 5 | The reports described transplant patients stabilized on cyclosporine, who presented reduced blood cyclosporine levels – associated, in some cases, with rejection episodes after taking therapeutic doses of St. John's wort. This is one of the best-documented, serious and potentially fatal interactions between a herbal remedy and a conventional drug. It likely occurs via induction of CYP3A4 and/or P-glycoprotein by St. John's wort. |
| | Digoxin | Decreased digoxin blood concentration (in 4 out of 5 studies) | Multiple pharmacokinetic trials [190, 191] Level of evidence: 4 | Digoxin has a narrow therapeutic index. Digoxin is a P-glycoprotein substrate. Extracts with a low hyperforin content had no effect on digoxin pharmacokinetics. |
| | Eletriptan | Serotonin syndrome | One case report [221] Level of evidence: 2 | Serotonin syndrome and rhabdomyolysis induced by the concomitant use of eletriptan, fluoxetine, and St. John's wort was reported in a 28-year-old woman. The authors believe that St. John's wort and fluoxetine, which both inhibit the re-uptake of 5-HT, predisposed the patient to developing a serotonin syndrome, which was precipitated by subsequent use of eletriptan, an antimigraine drug that binds to $5\text{-HT}_{1B}$ and $5\text{-HT}_{1D}$ receptors. |
| | Fexofenadine | Decreased fexofenadine blood concentration | Two pharmacokinetic trials [221] Level of evidence: 4 | Fexofenadine is a P-glycoprotein substrate. |
| | Gliclazide | Decreased gliclazide blood concentration | One pharmacokinetic trial [151] [see 143] Level of evidence: 4 | Gliclazide is a CYP2C9 probe. However, induction of this CYP isoform by St. John's wort is unlikely to explain such an interaction. |
| | Imatinib | Decreased imatinib blood concentration | Two pharmacokinetic trials [201, 202] Level of evidence: 4 | A decreased plasma concentration of imatinib drug following a 14-day treatment with the herbal product (300 mg 3 times daily) has been observed in 2 clinical trials. Induction of CYP34A by St. John's wort may explain such an interaction. |

**Table 1** (continued)

| Herbal medicine (common and Latin name) | Prescribed drug | Clinical result of interaction | Source of evidence Level of evidence (levels 1–5)[1] | Comment |
|---|---|---|---|---|
| St. John's wort *Hypericum perforatum* | Indinavir | Decreased indinavir blood concentration | One pharmacokinetic trial [198] Level of evidence: 4 | The trial showed that St. John's wort (extract standardized to 0.3% hypericin, 300 mg 3 times daily for 16 days) decreased plasma levels of indinavir in 8 volunteers. Induction of CYP34A by St. John's wort may explain such an interaction. In addition, a case of increased HIV RNA viral load after combining St. John's wort with indinavir and lamivudine has been mentioned in a review article [6]. |
| St. John's wort *Hypericum perforatum* | Irinotecan | Decreased blood levels of SN-38 (the active metabolite of irinotecan) | One pharmacokinetic trial [200] Level of evidence: 4 | The trial showed that 18 days' treatment with St. John's wort (300 mg twice daily for 18 days) markedly (42%) decreased the plasma levels of SN-38, the active metabolite of irinotecan, in 5 cancer patients. Induction of CYP34A by St. John's wort may explain such an interaction. |
| | Ivabradine | Decreased ivabradine blood concentration | One pharmacokinetic trial [195] Level of evidence: 4 | Induction of CYP34A by St. John's wort may explain such an interaction. |
| | Lamivudine | Increased HIV RNA viral load | One case report mentioned in a review article [6] Level of evidence: 1 | The patient was on lamivudine and indinavir therapy. |
| | Loperamide | Acute delirium | One case report [223] Level of evidence: 1 | The patient also took valerian *(V. officinalis)*. The interaction needs to be confirmed. The mechanism is unknown. |
| | Mephenytoin | Increased urinary excretion of mephenytoin metabolites | One pharmacokinetic trial [147] Level of evidence: 4 | St. John's wort (extract standardized to 0.3% hypericin and 4% hyperforin, 300 mg 3 times daily for 14 days) increased the urinary excretion of mephenytoin (a CYP2C19 substrate) metabolites in 12 male volunteers [147]. This interaction is suggestive of CYP2C19 induction. |
| | Methadone | Decreased methadone blood concentration | One clinical trial [216] Level of evidence: 4 | St. John's wort (Jarsin®, 900 mg daily for 31 days) reduced methadone plasma concentration in 4 drug-addicted patients. Two patients reported symptoms that suggested a withdrawal syndrome. Induction of CYP3A4 and/or P-glycoprotein by St. John's wort may explain this interaction. |
| | Midazolam | Decreased midazolam blood concentration | Multiple pharmacokinetic trials [55, 56, 146, 149] Level of evidence: 4 | Induction of intestinal (and possibly hepatic) CYP3A4 by St. John's wort may explain this interaction. |
| | Nefazodone | Serotonin syndrome | One case report [206] Level of evidence: 2 | A pharmacodynamic effect has been postulated (additive effect on 5-HT signalling). A serotonin syndrome has also been observed when St. John's wort was given along with other antidepressants that inhibit the re-uptake of serotonin (i.e. paroxetine, sertaline and venlafaxine). |
| | Nevirapine | Decreased nevirapine blood concentration | Two cases in one publication [199] Level of evidence: 3 | Induction of intestinal CYP3A by St. John's wort may explain this interaction. |
| | Nifedipine | Decreased nifedipine blood concentration | One pharmacokinetic trial [196] Level of evidence: 4 | Induction of intestinal CYP3A by St. John's wort may explain this interaction. |
| | Omeprazole | Decreased omeprazole blood concentration | One pharmacokinetic trial [154] Level of evidence: 4 | The interaction is suggestive of CYP2C19 induction by St. John's wort. |
| | Oral contraceptive | Changes in the pharmacokinetics of oral pill resulting in reduced efficacy; increased breakthrough bleeding | Multiple pharmacokinetic trials and multiple case reports [181–186] Level of evidence: 5 | A case of unwanted pregnancy has been reported. Induction of intestinal CYP3A by St. John's wort may explain this interaction. No pharmacokinetic interaction was observed in a trial in which an extract with low hyperforin was used. |

**Table 1** (continued)

| Herbal medicine (common and Latin name) | Prescribed drug | Clinical result of interaction | Source of evidence Level of evidence (levels 1–5)[1] | Comment |
|---|---|---|---|---|
| St. John's wort *Hypericum perforatum* | Paroxetine | Serotonin syndrome | One case report [207] Level of evidence: 3 | A pharmacodynamic effect has been postulated (additive effect on 5-HT uptake). A serotonin syndrome has also been observed when St. John's wort was given along with other antidepressants that inhibit the re-uptake of serotonin (i.e. sertraline, nefazodone and venlafaxine). |
| | Phenprocoumon | Decreased phenprocoumon blood concentration and pharmacological effect | One pharmacokinetic trial and one case report [162, 189] Level of evidence: 5 | Phenprocoumon is chemically related to warfarin. A similar interaction has been described for warfarin. |
| | Prednisone | Manic episode | One case report [179] Level of evidence: 1 | Because the patient was also an alcohol and cocaine addict and because both St. John's wort and prednisone may cause mania when administered alone, causality is very unlikely. On the other hand, a clinical trial showed that St. John's wort did not change the pharmacokinetics of prednisone in 8 male volunteers [180]. |
| | Rosuvastatin | Reduced efficacy of rosuvastatin | One pharmacokinetic trial [194] Level of evidence: 4 | St. John's wort reduces the blood levels of other statins such as simvastatin and atorvastatin. |
| | Quazepam | Decreased quazepam blood concentration | One pharmacokinetic trial [203] Level of evidence: 4 | Induction of intestinal CYP3A by St. John's wort may explain this interaction. |
| | Sertraline | Serotonin syndrome | A case series (4 cases) and a case report [206, 209] Level of evidence: 2 | A pharmacodynamic effect has been postulated (additive effect on 5-HT uptake). Serotonin syndrome has also been observed when St. John's wort was given along withother antidepressants that inhibit the re-uptake of serotonin (i.e. paroxetine, nefazodone and venlafaxine). |
| | Simvastatin | Decreased simvastatin blood concentration | One pharmacokinetic trial [192] Level of evidence: 4 | Induction of CYP3A4 and/or P-glycoprotein by St. John's wort may explain this interaction. |
| | Tacrolimus | Decreased tacrolimus blood concentration | A case report and two pharmacokinetic trials [149, 158] Level of evidence: 5 | Induction of CYP3A4 and/or P-glycoprotein by St. John's wort may explain this interaction. |
| | Talinolol | Reduced talinolol blood concentration | One pharmacokinetic trial [197] Level of evidence: 4 | Tanilolol is a P-glycoprotein probe. |
| | Theophylline | Decreased theophylline blood concentration | One case report [219] Level of evidence: not applicable | This interaction has not been confirmed by a pharmacokinetic trial. |
| | Tibolone | Acute hepatitis | A case report [187] Level of evidence: 2 | Acute hepatitis with prolonged cholestasis and disappearance of interlobular bile ducts was observed in a 57-year-old woman who had been taking St. John's wort (extract type not specified) for 10 weeks in combination with tibolone, a synthetic steroid hormone drug licensed for the relief of climacteric symptoms and the prevention of osteoporosis in postmenopausal women [187]. The mechanism is unknown. The interaction needs to be confirmed. |
| | Venlafaxine | Serotonin syndrome | One case report [see 143] Level of evidence: 3 | A pharmacodynamic effect has been postulated (additive effect on 5-HT uptake). The report was well documented and appeared to provide reliable evidence. A serotonin syndrome has also been observed when St. John's wort was given along with other antidepressants that inhibit the re-uptake of serotonin (i.e. paroxetine, nefazodone and sertraline). |
| | Verapamil | Decreased verapamil blood concentration | One pharmacokinetic trial [143] Level of evidence: 4 | Induction of intestinal CYP3A4 by St. John's wort may explain this interaction. |

**Table 1** (continued)

| Herbal medicine (common and Latin name) | Prescribed drug | Clinical result of interaction | Source of evidence Level of evidence (levels 1–5)[1] | Comment |
|---|---|---|---|---|
| St. John's wort *Hypericum perforatum* | Voriconazole | Transient increase followed by a decreased blood concentration | One pharmacokinetic trial [213] Level of evidence: 4 | Voriconazole is a CYP2C19 substrate. |
| | Warfarin | Increased warfarin clearance and decreased anticoagulant effect | One pharmacokinetic trial [95] and seven cases in one publication [see 8] Level of evidence: 5 | A similar interaction has been described for phenprocoumon (an analogue of warfarin). |
| St. John's wort *Hypericum perforatum* | Zolpidem | Decreased zolpidem blood concentration | One pharmacokinetic trial [204] Level of evidence: 4 | St. John's wort decreases blood levels of zolpidem, probably by enhancing CYP3A4 activity. |
| Valerian *Valeriana officinalis* | Loperamide | Acute delirium | One case report [223] Level of evidence: 1 | The patient also took valerian and St. John's wort. The interaction needs to be confirmed. The mechanism is unknown. |
| | Lorazepam | Hand tremor, dizziness, throbbing and muscular fatigue | One case report [222] Level of evidence: 2 | The patients also took passion flower. Taken along with the benzodiazepine lorazepam, both valerian and passion flower may exert an additive CNS-depressant effect. |

[1] The levels of evidence are specified in 'Materials and Methods'. [2] Red yeast rice is produced by fermentation of cooked rice using the fungus *Monascus purpureus*.

The concomitant use of prescription medications and herbal products by older adults is a common situation in western countries [243]. In addition, because older adults have multiple health problems, they are at particular risk for herb-to-drug interactions. Despite this, clinical studies aimed at investigating the potential of drug interaction in elderly patients are rare. Gurley et al. [55] found that elderly subjects, like their younger counterparts, are susceptible to herb-mediated changes in CYP activity and that some age-related changes in CYP responsivity to herbal products may exist. Specifically, it was found that ginseng slightly inhibited CYP2D6 in elderly subjects [55], in contrast to young subjects where no such inhibition was observed [56].

It is well established that the pharmacokinetics of many drugs may vary between men and women. Gender differences in herb-to-drug interactions have been reported both experimentally and in clinical trials. For example, a differential inductive profile of hepatic cytochrome P450s by the extracts of *Sophora flavescens* in male and female mice have recently been observed [244]. More importantly, Gurley et al. [56] reported a significant sex-related difference in the inductive ability of St. John's wort on CYP3A4 activity (i.e. St. John's wort induced CYP3A4 more marked in male than in female subjects).

## Patient Counselling

The use of herbal medicines is widespread. A survey found that approximately 15% of patients receiving conventional pharmacotherapy also take herbal products, and among these, potential adverse herb-to-drug interactions were observed in 40% of patients [245]. It is therefore incumbent upon health care professionals to ask their patients about their use of herbal remedies. Patients erroneously believe that herbal products are natural and therefore safe. Probably for this reason, they are reluctant to disclose fully herbal use to their physicians. A recent study found that only 51.8% of women using complementary medicine, including herbal medicine, disclosed this use to their physician [246]. It is therefore imperative that patients, especially those under cardiovascular, immunosuppressant or antiretroviral therapy, be informed of the possible adverse effects caused by interactions between herbal products and conventional medicines.

## Limitations

This review article has several limitations: interactions were searched by consulting PubMed and Embase and by checking the reference list of relevant review articles dealing with herb-to-drug interactions. Only clinical reports were considered. Preclinical studies, including human in vitro experiments, were not considered. Even though the search strategy was meticulous, the author cannot affirm that all relevant clinical data have been retrieved.

A good deal of the evidence on herb-to-drug interactions discussed in this article is based on case reports, which are sometimes incomplete and do not allow one to infer a causal relationship. It is worth noting that even documented case reports can never establish a causal relationship between drug administration and an adverse event; in addition for many interactions listed in table 1, the evidence is far from conclusive, as sometimes only one case report has been used and in many cases, a poorly documented case report may have been published. In this article, the level of evidence has been categorized using a 5-point scoring system. The highest level of clinical evidence (i.e. level of evidence: 5) has been considered when an adverse event described in a case report has been confirmed by a clinical pharmacokinetic trial. On the other hand, many adverse events are supported by poorly documented case reports (level of evidence 1, see table 1 for further details). When pharmacokinetic trials have not confirmed the adverse event hypothesized on the basis of the published case report(s) (e.g. interactions between warfarin and cranberry or ginkgo) or when contradictory pharmacokinetic data were published, the level of evidence was defined as 'not applicable'. Although this scale has not been validated, it may be helpful as a guide for assessing whether an interaction is supported by adequate reliable clinical information.

In many instances, the extract type, standardization of extract, part of the plant used and the scientific (Latin) name of the plant have not been specified in clinical papers. This is an important omission because preparations obtained from the same plant may have different chemical compositions and hence different biological actions. Herbal preparations are not subject to the same regulations as prescription drugs and thus the content of the active ingredients may vary among manufacturers, potentially causing a large variation in efficacy and safety [247, 248].

The often underregulated quality of herbal medicines is another safety issue. Contamination or adulteration of herbal medicines, including adulteration with synthetic drugs, may be relatively frequent and can cause drug interactions [2, 3]. In other words, the possibility that a contaminant/adulterant and not an herbal ingredient causes drug interactions cannot be ruled out.

As highlighted above, people who use herbal medicines tend to conceal this use to their physicians or pharmacists. This observation, together with the fact that in many countries there are no central mechanisms for mandatory reporting as there is for conventional medicine complicate the identification of most herb-to-drug interactions.

## Conclusion

Clinical reports clearly indicate that herbal medicines can interact with conventional drugs. While the majority of such interactions may have a negligible clinical significance, some may pose a serious threat to public health. For example, combining St. John's wort with antiretroviral, immunosuppressive or anticancer agents that are metabolized by CYP enzymes and/or are substrates of P-glycoprotein may lead to drug failure. Serious health problems may occur when patients take herbal products before surgery. Cases of delayed emergence, cardiovascular collapse and loss of blood have been documented. A recent retrospective review of surgery patients presenting to the Anesthesia Preoperative Evaluation Clinic at the University of Kansas Hospital reported that approximately one-fourth of patients indicated the use of natural products prior the surgery [249]. It is therefore incumbent on clinicians to screen patients before surgery for use of these supplements.

In conclusion, herbal medicines may be used by patients concomitantly receiving conventional drugs, which can result in potentially serious adverse events. It is incumbent upon healthcare professionals to be well informed about the growing clinical evidence of herb-to-drug interactions.

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