# Herb–drug interactions: Review and assessment of report reliability

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***Aims*** The aim of this systematic review was to assess the published clinical evidence on interactions between herbal and conventional drugs.

***Methods*** Four electronic databases were searched for case reports, case series or clinical trials of such interactions. The data were extracted and validated using a scoring system for interaction probability.

***Results*** One hundred and eight cases of suspected interactions were found. 68.5% were classified as 'unable to be evaluated', 13% as 'well-documented' and 18.5% as 'possible' interactions. Warfarin was the most common drug (18 cases) and St John's wort the most common herb (54 cases) involved.

***Conclusion*** Herb–drug interactions undoubtedly do occur and may put individuals at risk. However our present knowledge is incomplete and more research is urgently needed.

*Keywords:* alternative medicine, herbal medicine, interaction, risk, safety

## Introduction

The popularity of herbal medicinal products (HMPs) makes it important to understand potential interactions between herbs and prescribed drugs. The likelihood of herb–drug interactions could be higher than drug–drug interactions, if only because drugs usually contain single chemical entities, while almost all HMPs (even single-herb products) contain mixtures of pharmacologically active constituents. The aim of this systematic review is to assess the clinical evidence on interactions between HMPs and drugs.

## Methods

The following databases were searched from their inception to the end of 2000: Medline, (via Pubmed), Embase, the Cochrane Library, CISCOM (a database specializing in the 'grey' literature pertaining to alternative medicines). Search terms were herbal medicine, botanical medicine, phytotherapy, adverse-effects, side-effects and drug interactions. Ten major manufacturers of herbal products were asked for (any type of) data on interactions. Eight experts and 24 organizations related to medical herbalism were invited to contribute further material. Four major reference texts [1–4], six recent review articles related to herbalism [5–10], our own extensive files, and the bibliographies of all articles thus found were also searched. There were no restrictions as to the language of publication. All reports of interactions were validated and extracted in a standardized form (Table 1).

A 10-point scoring system for interaction probability was devised. This scale has not been validated but we provide it only as a guide for assessing whether reports of herb–drug interactions contain adequately reliable information.

### *Report reliability scale for drug interactions*

Reports were given one point for each of the following:

- Adequate patient history (including age, sex, relevant medical conditions)
- Concurrent diseases, conditions, or medications associated with an adverse event
- Concomitant medications are documented
- Description of interactors is adequate
- Obvious alternative explanations have been excluded
- Chronology is complete
- Time sequence of drug administration to adverse event is reasonable

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*Received 25 November 2000, accepted 29 June 2001.*

 

**Table 1** Case reports of herb/drug interactions.

| *Patient description (reference)* | *Herb Latin name (Common use)* | *Drug* | *Other medications* | *Signs or symptoms of interaction* | *Mechanism* | *Report reliability score* |
|---|---|---|---|---|---|---|
| 51 year old man with schizophrenia [38] | Betel nut *Areca catechu* (Stimulant) | Fluphenazine | Procyclidine | Rigidity, bradykinesia, jaw tremor | Not known | Likely 1+1+1+1+1+1 +1+1+1+0=9 |
| 45 year old man with schizoaffective disorder | Betel nut *Areca catechu* (Stimulant) | Flupenthixol | Procyclidine | Stiffness, tremor, akathisia | Not known | Likely 1+1+1+1+1+1+1 +1+1+0+=9 |
| 53 year old woman [39] | Chili pepper (*Capsicum* species) (Pain) | ACE inhibitor | None mentioned | Recurrent cough only after application of topical capsaicin 0.075% cream | Not known | Possible 0+0+0+0+1+1 +0+1+1+1=5 |
| 66 year old man with atrial fibrillation, rheumatic mitral stenosis, cerebral embolism, and gastric adenocarcinoma [40] | Danshen *Salvia miltiorrhiza* (Cardiovascular disease) | Warfarin | Digoxin, propranolol, topical oil containing 15% salicylates | ↑ INR; gastric bleeding but additive action due to coumarin content of herb | Probably no interaction | Possible 1+0+1+1+1+0+1 +1+1+0+0=6 |
| 62 year old man with mitral valve replacement [41] | Danshen *Salvia miltiorrhiza* (Cardiovascular disease) | Warfarin | Digoxin, frusemide, captopril | ↑ INR but additive action due to coumarin content of herb | Probably no interaction | Likely 1+1+1+1+1+1+1 +1+1+1+0=9 |
| 48 year old woman with a history of rheumatic heart disease, mitral stenosis and atrial fibrillation [42] | Danshen *Salvia miltiorrhiza* (Cardiovascular disease) | Warfarin | Digoxin frusemide, theophylline, mefenamic acid | ↑ INR but additive action due to coumarin content of herb | Probably no interaction | Possible 1+1+1+0+0+0 +0+1+0+0=4 |
| No information provided [43] | Devil's claw *Harpargo-phytum-procumbens* (Arthritis) | Warfarin | Purpura | | Herb acts as Cox inhibitor | Unevaluable =0 |
| 46 year old woman with history of stroke, rheumatic heart disease and atrial fibrillation [44] | Dong quai *Angelica sinensis* (Gynaecological conditions) | Warfarin | Digoxin, frusemide | ↑ INR | Herb acts as Cox inhibitor | Likely 1+1+1+1+1+1+1 +1+1+1+0=9 |
| Woman with history of mitral valve replacement [45] | Dong quai *Angelica sinensis* (Gynaecological conditions) | Warfarin | None stated | INR = 10, widespread bruising | Herb acts as Cox inhibitor | Possible 0+0+0+0+0+1 +1+1+0+0=3 |

 

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| 74 year old man with atrial fibrillation [46] | Eleuthero (Siberian ginseng) *Eleutherococcus senticosis* (Fatigue) | Digoxin | Acetaminophen, cimetidine, oxazepam, aspirin, magaldrate | Elevated digoxin concentration | Probable interference with assay rather than drug | Likely 1+1+1+1+1+1 +1+1+1+1=10 |
| No information provided [46] | Evening primrose oil *Oenethera biennis* (Premenstrual syndrome, other gynaecological conditions) | Anaesthetics | 'Other pharmaceuticals' | Seizures | Not known | Unevaluable 0 |
| Two patients, no details provided [47] | Garlic *Allium sativum* (Hypercholesterolaemia) | Warfarin | None | Increased INR, increased clotting time | Herb has antiplatelet activity | Unevaluable 0 |
| 80 year old Alzheimer's patient [48] | Ginkgo *Ginkgo biloba* (Circulatory disorders) | Trazodone | Bromazepam, donepezil, vitamin E discontinued within 3 days | Coma | Herb has antiplatelet activity | Possible 1+0+1+1+0+1 +1+1+0+0=6 |
| 78 year old woman with history of hypertension, myocardial infarction, atrial fibrillation, coronary bypass, and gait problems [49] | Ginkgo *Ginkgo biloba* (Circulatory disorders) | Warfarin | None stated | PT16.9, PTT35.5, left parietal haemorrhage | Herb has antiplatelet activity | Possible 1+0+0+0+0+1 +1+1+0+0=4 |
| 70 year old man with history of coronary artery bypass (no other details) [50] | Ginkgo *Ginkgo biloba* (Circulatory disorders) | Aspirin | None stated | Spontaneous hyphema (bleeding into the iris) | Herb has antiplatelet activity | Possible 0+0+0+1+0+1 +1+1+0+0=4 |
| Elderly woman with hypertension (no other details) [46] | Ginkgo *Ginkgo biloba* (Circulatory disorders) | Thiazide diuretic | None stated | Increased blood pressure | Not known | Unevaluable 0+0+0+0+0+0 +1+0+0+0=1 |
| 47 year old man with history of heart valve replacement [51] | Ginseng *Panax* species (Fatigue) | Warfarin | Diltiazem nitroglycerin, salsalate | INR decreased to 1.5 (previously stable 2–3) | Herb has antiplatelet activity | Likely 1+1+1+1+1+1 +1+1+1+0=9 |
| 42 year old woman with chronic depression [52] | Ginseng *Panax* species (Fatigue) | Phenelzine | Lorazepam triazolam, bee pollen | Manic symptoms | Not known | Possible 1+1+1+0+0+0 +0+1+0+0=4 |
| 64 year old woman [53] | Ginseng *Panax* species (Fatigue) | Phenelzine | None | Insomnia, headache, tremor | Not known | Unevaluable 0+0+0+0+0+0 +0+1+0+1=2 |
| 76 year old woman with Parkinson's disease [54] | Kava *Piper methysticum* (Anxiety) | Levodopa | Benserazide | Increased number and duration of 'off' periods | Not known | Likely 1+1+1+1+1+1 +1+1+1+0=9 |
| 54 year old man [55] | Kava | Alprazolam | Cimetidine, terazosin | Lethargy, disorientation ×several hours | Probably no interaction but additive effects | Unevaluable 0+0+1+0+0+0 +1+1+0+0=3 |

 

**Table 1** (Cont.).

| *Patient description (reference)* | *Herb Latin name (Common use)* | *Drug* | *Other medications* | *Signs or symptoms of interaction* | *Mechanism* | *Report reliability score* |
|---|---|---|---|---|---|---|
| Male admitted for cardiac surgery [46] | Papaya extract *Papaya carica* (Indigestion, weight loss) | Warfarin | None mentioned | ↑ INR | Not known | Unevaluable 0+0+0+0+0+0+0+1+1+0=2 |
| 42 year old woman with depression and numerous other symptoms [56] | St John's wort *Hypericum perforatum* (Depression) | Theophylline | Frusemide, potassium, morphine, zolpidem, valproic acid, ibuprofen, amitriptyline, albuterol, prednisolone, zafirlukast, triamcinolone | ↓ Theophylline concentrations | Induction of cytochrome P450 | Possible 0+0+1+1+1+0+0+0+1+0=4 |
| 44 year old woman with kidney transplant, and 29 year old woman with kidney and pancreas transplant [57] | St John's wort *Hypericum perforatum* (Depression) | Cyclosporin | Mycophenoloate (44 years old); prednisone (29 years old) | ↓ cyclosporin concentrations in both; acute cellular rejection in 29 years old | Induction of cytochrome P450 | Likely (1+1+1+1+1+1+1+1+1+0=9), (1+1+1+1+1+1+1+1+0+0=8) |
| 63 year old patient 14 months after liver transplant [58] | St John's wort *Hypericum perforatum* (Depression) | Cyclosporin | Acetyldigoxin | Liver transplant rejection 2 week p SJW | Induction of cytochrome P450 | Likely 1+1+1+1+1+1+1+1+1+0=9 |
| Kidney transplant patient [59] | St John's wort *Hypericum perforatum* (Depression) | Cyclosporin | Benzbromarone, betaxolol, amlodipine, pravastatin, magnesium | ↓ cyclosporin concentrations | Induction of cytochrome P450 | Likely 1+1+1+1+1+1+1+1+1+1=10 |
| Case series $n=45$ [60] 35 kidney transplant recipients and 10 liver transplant recipients (subset case series $n=30$ kidney recipients published elsewhere) [61] | St John's wort *Hypericum perforatum* (Depression) | Cyclosporin | None mentioned | Cyclosporin concentrations ↓ 30–64%; 2 rejection episodes | Induction of cytochrome P450 | Unevaluable |
| 61 year old male 11 months after heart transplant [62] | St John's wort *Hypericum perforatum* (Depression) | Cyclosporin | Azathioprine, corticosteroids | Evidence of tissue rejection ↓ cyclosporin levels | Induction of cytochrome P450 | Likely 1+1+1+1+1+1+1+1+1+0=9 |
| 63 year old male 20 months after heart transplant [65] | St John's wort *Hypericum perforatum* (Depression) | Cyclosporin | 'Standard immunosuppressive regimen' | Evidence of tissue rejection ↓ cyclosporin concentrations | Induction of cytochrome P450 | Likely 1+1+1+1+1+1+1+1+1+0=9 |
| Woman in her mid-twenties (no other information provided) [63] | St John's wort *Hypericum perforatum* (Depression) | Cyclosporin | None mentioned | Cyclosporin concentrations ↓ 75% | Induction of cytochrome P450 | Unevaluable 0+0+0+0+0+0+0+0+1+0+0=1 |

 

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|---|---|---|---|---|---|---|
| 61 year old woman 10 months post heart transplant [64] | St John's wort *Hypericum perforatum* (Depression) | Cyclosporin | None mentioned | Rejection episode, decreased cyclosporin concentrations | Induction of cytochrome P450 | Possible 1+1+0+1+1+1 +1+0+0+0=6 |
| 54 year old woman with lung fibrosis [67] | St John's wort *Hypericum perforatum* (Depression) | Cyclosporin | Prednisolone | ↓ cyclosporin concentrations | Induction of cytochrome P450 | Possible 1+1+1+1+1+0 +0+1+1+0=7 |
| 74 year old woman [67] | St John's wort *Hypericum perforatum* (Depression) | Phenpro-coumon | None mentioned | ↑ 'Quick-Wert' test (indicating decreased anticoagulant effect) | Induction of cytochrome P450 | Possible 0+0+0+1+1+1 +1+1+1+0=6 |
| Case series $n=7$ [65] (age 56–85 years, 4 female, no other information provided) | St John's wort *Hypericum perforatum* (Depression) | Warfarin | None mentioned | 6 cases ↓ INR 1 case ↓ INR | Induction of cytochrome P450 | Unevaluable 1–2 |
| Case series $n=3$ All women described as long-term users of COCs; one was 44 years old; no other ages or other information provided [67] | St John's wort *Hypericum perforatum* (Depression) | Combined oral contraceptive (ethinyloestradiol and desogestrel) | None mentioned | Intermenstrual (breakthrough) bleeding | Induction of cytochrome P450 | Unevaluable 0+0+0+1+0+0 +1+1+0+0=3 |
| Case series $n=9$ women 23–31 years old (no other information provided) [68] | St John's wort *Hypericum perforatum* (Depression) | Combined oral contraceptives | None mentioned | Intermenstrual bleeding [8] and 'changed menstrual bleeding' [1] | Induction of cytochrome P450 | Unevaluable |
| 61 year old woman [66] | St John's wort *Hypericum perforatum* (Depression) | Paroxetine | None mentioned | Serotonin syndrome (akithisia, hyperreflexia, diaphoresis, hypertension, tachycardia) | Probably additive effects only | Possible 1+1+0+0+0+1 +1+1+1+0=6 |
| 50 year old woman with asthma and depression [67] | St John's wort *Hypericum perforatum* (Depression) | Paroxetine | None mentioned | Lethargy, nausea and fatigue ×several hours | Probably additive effects only | Possible 1+1+1+1+1+10 +0+0+0=6 |
| 29 year old depressed man with cardiac conduction defect, previous bilateral orchidectomy [68] | St John's wort *Hypericum perforatum* (Depression) | Sertraline | Testosterone | Mania | Probably additive effects only | Possible 1+0+1+0+0+1 +1+1+0+0=5 |
| 78 year old woman with depression [69] | St John's wort *Hypericum perforatum* (Depression) | Sertraline | 'Included' calcium carbonate, conjugated oestrogens★ | Dizziness, nausea, vomiting, headache | Probably additive effects only | Possible 1+1+1+0+1+0 +1+1+1+0=7 |
| 64 year old man with depression [69] | St John's wort *Hypericum perforatum* (Depression) | Sertraline | None mentioned | Nausea, epigastric pain, anxiety | Probably additive effects only | Possible 1+1+1+0+1+0 +1+1+1+0=7 |
| 82 year old man with history of depression and VVA [69] | St John's wort *Hypericum perforatum* (Depression) | Sertraline | 'Included' aspirin, multivitamins★ | Nausea, vomiting, anxiety, confusion | Probably additive effects only | Possible 1+1+1+0+1+0+1 +1+1+0=7 |

**Table 1** (Cont.).

| *Patient description (reference)* | *Herb Latin name (Common use)* | *Drug* | *Other medications* | *Signs or symptoms of interaction* | *Mechanism* | *Report reliability score* |
|---|---|---|---|---|---|---|
| 79 year-old-man with diabetes and depression [69] | St John's wort *Hypericum perforatum* (Depression) | Sertraline | Insulin | Nausea, anxiety, restlessness, irritability | Probably additive effects only | Unevaluable $1+1+0+0+0+0+1+0+0+0=3$ |
| 84 year old woman with depression and anxiety [69] | St John's wort *Hypericum perforatum* (Depression) | Nefazodone | None mentioned | Nausea, vomiting, restlessness | Probably additive effects only | Possible $1+1+0+0+0+0+0+1+1+1+0=5$ |
| 32 year old woman with depression [70] | St John's wort *Hypericum perforatum* (Depression) | Venlaxafine | None mentioned | Malaise, sweating, tremor, tachycardia within 3 days | Probably additive effects only | Likely $1+1+0+1+1+1+1+1+1+0=8$ |
| 39 year old woman with depression and migraine [71] | St John's wort *Hypericum perforatum* (Depression) | Loperamide | Valerian | Disorientation, agitation, confusion | Probably additive effects only | Possible $1+1+1+0+0+0+0+1+0+0=4$ |

- Adverse event is adequately described
- Event ceases on stopping the drug
- Event recurs on rechallenge

*Scoring*

- 0–3 Unevaluable – report contains inadequate information to assess the likelihood of an interaction
- 4–7 Possible – report provides some evidence for an interaction, but there may be other causes of the event
- 8–10 Likely – the report is well documented and appears to provide reliable evidence for an interaction.

## Results

One hundred and eight cases of suspected interactions were identified (Table 1). Seventy-four of these (68.5%) did not contain sufficient information to evaluate the likelihood of an interaction. Fourteen (13%) of the reports were classified as well-documented, and 20 (18.5%) as possible. Warfarin was the most common drug involved (18 cases of which 61% were considered unevaluable). St John's wort was the herb most commonly implicated in interactions, and a total of 85 cases have been reported, of which 54 cases or 63.5% were with cyclosporin. Other reports involving St John's wort included 12 cases of interactions with oral contraceptives, seven with warfarin, nine with antidepressants, and one each with phenprocoumon, theophylline, and loperamide. Seven case reports (8.2%) were considered well-documented.

## Discussion

Clinical studies have documented that St John's wort lowers serum concentrations of digoxin [11], phenprocoumon [12], indinavir [13], amitriptyline, and nortriptyline [14]. A recent study found no effect of St John's wort (300 mg standardized to 0.3% hypericin three times daily (14 days)) on carbamazepine pharmacokinetics [15]. *Piper longum* contains piperine, which has been shown in clinical trials to increase $C_{max}$ and AUC of phenytoin [16], propranolol, and theophylline [17].

Three clinical studies have examined interactions of psychoactive herbs with alcohol. One study found that mixed valepotriates from *Valeriana officinalis* reduced the adverse effect of alcohol on concentration [18]. Another demonstrated that *Panax ginseng* enhanced alcohol clearance in humans [19]. A clinical study of an infusion of *Piper methysticum* found that kava potentiates impairment when combined with alcohol [20].

The effect of *Catha edulis* on the pharmacokinetics of single-dose ampicillin and amoxicillin has been studied. The bioavailability of the latter was reduced significantly

during a khat-chewing session, but no effect was noted with amoxicillin [21].

Licorice (*Glycyrrhiza glabra*) contains glycyrrhizin, which inhibits 11β-dehydrogenase, 5α-reductase, and 5β-reductase. Glycyrrhizin is metabolized largely to glycyrrhetinic acid (an even more potent inhibitor of 5α-, 5β-reductase and 11β-dehydrogenase). Liquorice has been shown to increase plasma concentrations of prednisolone [22, 23]. It also potentiated the cutaneous vasoconstrictor response of hydrocortisone [24]. Licorice is a common herb in Chinese and Japanese herbal mixtures. The effect of several such mixtures on prednisolone concentrations has been tested. Both Sho-saiko-To and Xiao Chai Hu Tang decreased the plasma AUC of prednisolone [25] whereas Saiboku-To increased it. Sairei-To did not affect it [26]. Both Sho-saiko-To and Rikkunshi-to were found not to affect the pharmacokinetics of a single oral dose of ofloxacin [26].

St John's wort affects the clearance of many drugs, including cyclosporin, antidepressants (predominantly SSRIs), digoxin, indinavir, and phenprocoumon. The underlying mechanism appears to be multifactorial. There is evidence of a strong interaction with P-glycoprotein (PgP), an ATP-dependent drug efflux transporter known to pump drugs out of the cell membrane, thus decreasing intracellular concentrations [27]. St John's wort increases expression of duodenal PgP/MDR1 [28]. The herb also induces the activity of an important form of cytochrome P450, CYP3A4. However, results of studies of the effect of St John's wort on CYP3A4 are conflicting. While three enzyme marker studies indicated a potent inducing effect of St John's wort (300 mg three times daily × 14 days) on CYP3A4 activity [29, 30], two others found no effect (both 300 mg three times daily, one for 3 days [31], the other for 8 days [32]) on CYP2D6 or 3A4 activities. It is possible that the negative trials were simply too short in duration. Alternatively, differences in quality of the HMPs used might explain the discrepancy. One study examining the effect of St John's wort on CYP1A2 activity (using a caffeine/dextromethorphan probe) found that it (300 mg three times daily for 8 days) had no effect on 17 DMX/caffeine ratios [33], indicating that this HMP has a low potential for drug interactions involving CYP 1A2.

Cases of serotonin syndrome could arise if St John's wort increased serotonin levels. However, it cannot be considered an SSRI, because *in vitro*, St John's wort inhibits the uptake of serotonin, noradrenaline and dopamine only at high concentrations with $IC_{50}$s of 2.4, 4.5, and 0.9 $\mu g\ ml^{-1}$, respectively [34] which are unlikely to be achieved with oral dosing. However, enough cases of interactions with SSRIs have been reported that a serotonergic (or serotonin-amplifying) effect of St John's wort could occur.

There is reasonable documentation of interactions between coumarin anticoagulants and St John's wort, danshen, dong quai, ginseng, and ginkgo [35]. Most of these case reports are probably not true interactions but result from additive anticoagulant effects. Dong quai contains coumarins, and would be expected to augment the effects of a coumarin-derived anticoagulant. Ginkgo and garlic interfere with platelet function, and have been associated with bleeding even in the absence of warfarin or other anticoagulant treatment. Danshen also interferes with platelet function but appears to decrease the elimination of warfarin at least in rats [37]. In a recent case report, the INR of a patient taking warfarin who drank 0.5–1 gallon of green tea (*Camellia sinensis*) was seen to decrease [36].

Inadequate reporting makes it difficult to determine whether a herb–drug interaction has occurred. Authors should be required to document all relevant information (see above). The adverse event should be clearly described, alternative explanations should be explored and a rechallenge should be considered. The HMP should be analysed to ascertain the contents of the product. Even well-documented case reports can only serve as a critical early warning system.

Herb–drug interactions occur but are under-researched. In many cases there is no plausible mechanism to explain the observed phenomena and causality is uncertain. Patients taking St John's wort or anticoagulants are at the highest risk of an interaction. Patients on coumarin anticoagulants should be specifically advised to avoid taking herbal medicines or to have their INR measured within 2 weeks of starting the product. Patients taking garlic, ginkgo, danshen, or other HMPs affecting platelet function should also be monitored. The risks of combining St John's wort with drugs or anticoagulant drugs with herbal medicines should be publicised further.

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