

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, CISCOS (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.

<i>Patient description (reference)</i>	<i>Herb Latin name (Common use)</i>	<i>Drug</i>	<i>Other medications</i>	<i>Signs or symptoms of interaction</i>	<i>Mechanism</i>	<i>Report reliability score</i>
51 year old man with schizophrenia [38]	Betel nut <i>Areca catechu</i> (Stimulant)	Fluphenazine	Procyclidine	Rigidity, bradykinesia, jaw tremor	Not known	Likely 1+1+1+1+1+1+1 +1+1+1+0=9
45 year old man with schizoaffective disorder	Betel nut <i>Areca catechu</i> (Stimulant)	Flupenthixol	Procyclidine	Stiffness, tremor, akathisia	Not known	Likely 1+1+1+1+1+1+1+1 +1+1+0+=9
53 year old woman [39]	Chili pepper <i>(Capsicum species)</i> (Pain)	ACE inhibitor	None mentioned	Recurrent cough only after application of topical capsaicin 0.075% cream	Not known	Possible 0+0+0+0+0+1+1 +0+1+1+1+1=5
66 year old man with atrial fibrillation, rheumatic mitral stenosis, cerebral embolism, and gastric adenocarcinoma [40]	Danshen <i>Salvia miltiorrhiza</i> (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+0+0+1 +1+1+0+0=6
62 year old man with mitral valve replacement [41]	Danshen <i>Salvia miltiorrhiza</i> (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 <i>Salvia miltiorrhiza</i> (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 +0+1+0+0=4
No information provided [43]	Devil's claw <i>Harpago-phytum-procumbens</i> (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 <i>Angelica sinensis</i> (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 <i>Angelica sinensis</i> (Gynaecological conditions)	Warfarin	None stated	INR = 10, widespread bruising	Herb acts as Cox inhibitor	Possible 0+0+0+0+0+0+1 +1+1+0+0=3

74 year old man with atrial fibrillation [46]	Eleuthero (Siberian ginseng) <i>Eleutherococcus senticosus</i> (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 + 1 = 10
No information provided [46]	Evening primrose oil <i>Oenothera biennis</i> (Premenstrual syndrome, other gynaecological conditions)	Anaesthetics	'Other pharmaceuticals'	Seizures	Not known	Unevaluable 0
Two patients, no details provided [47]	Garlic <i>Allium sativum</i> (Hypercholesterolaemia)	Warfarin	None	Increased INR, increased clotting time	Herb has antiplatelet activity	Unevaluable 0
80 year old Alzheimer's patient [48]	Ginkgo <i>Ginkgo biloba</i> (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 <i>Ginkgo biloba</i> (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 <i>Ginkgo biloba</i> (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 <i>Ginkgo biloba</i> (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 <i>Panax species</i> (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 <i>Panax species</i> (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 <i>Panax species</i> (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 <i>Piper methysticum</i> (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 <i>Papaya carica</i> (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 <i>Hypericum perforatum</i> (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+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 <i>Hypericum perforatum</i> (Depression)	Cyclosporin	Mycophenolate (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+1+0=9), (1+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 <i>Hypericum perforatum</i> (Depression)	Cyclosporin	Acetyldigoxin	Liver transplant rejection 2 week p SJW	Induction of cytochrome P450	Likely 1+1+1+1+1+1+1 +1+1+1+0=9
Kidney transplant patient [59]	St John's wort <i>Hypericum perforatum</i> (Depression)	Cyclosporin	Benzbromarone, betaxolol, amlodipine, pravastatin, magnesium	↓ cyclosporin concentrations	Induction of cytochrome P450	Likely 1+1+1+1+1+1+1 +1+1+1+1=10
Case series <i>n</i> = 45 [60] 35 kidney transplant recipients and 10 liver transplant recipients (subset case series <i>n</i> = 30 kidney recipients published elsewhere) [61]	St John's wort <i>Hypericum perforatum</i> (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 <i>Hypericum perforatum</i> (Depression)	Cyclosporin	Azathioprine, corticosteroids	Evidence of tissue rejection ↓ cyclosporin levels	Induction of cytochrome P450	Likely 1+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 <i>Hypericum perforatum</i> (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+1+0=9
Woman in her mid-twenties (no other information provided) [63]	St John's wort <i>Hypericum perforatum</i> (Depression)	Cyclosporin	None mentioned	Cyclosporin concentrations ↓ 75%	Induction of cytochrome P450	Unevaluable 0+0+0+0+0+0+0 +0+1+0+0=1

61 year old woman 10 months post heart transplant [64]	St John's wort <i>Hypericum perforatum</i> (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 <i>Hypericum perforatum</i> (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 <i>Hypericum perforatum</i> (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 <i>n</i> = 7 [65] (age 56–85 years, 4 female, no other information provided)	St John's wort <i>Hypericum perforatum</i> (Depression)	Warfarin	None mentioned	6 cases ↓ INR 1 case ↓ INR	Induction of cytochrome P450	Unevaluable 1–2
Case series <i>n</i> = 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 <i>Hypericum perforatum</i> (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 <i>n</i> = 9 women 23–31 years old (no other information provided) [68]	St John's wort <i>Hypericum perforatum</i> (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 <i>Hypericum perforatum</i> (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 <i>Hypericum perforatum</i> (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 <i>Hypericum perforatum</i> (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 <i>Hypericum perforatum</i> (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 <i>Hypericum perforatum</i> (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 <i>Hypericum perforatum</i> (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 <i>Hypericum perforatum</i> (Depression)	Sertraline	Insulin	Nausea, anxiety, restlessness, irritability	Probably additive effects only	Unevaluable 1+1+0+0+0+0+0+1 +0+0+0+0=3
84 year old woman with depression and anxiety [69]	St John's wort <i>Hypericum perforatum</i> (Depression)	Nefazodone	None mentioned	Nausea, vomiting, restlessness	Probably additive effects only	Possible 1+1+0+0+0+0+0 +1+1+1+1+0=5
32 year old woman with depression [70]	St John's wort <i>Hypericum perforatum</i> (Depression)	Venlafaxine	None mentioned	Malaise, sweating, tremor, tachycardia within 3 days	Probably additive effects only	Likely 1+1+0+1+1+1+1 +1+1+1+1+0=8
39 year old woman with depression and migraine [71]	St John's wort <i>Hypericum perforatum</i> (Depression)	Loperamide	Valerian	Disorientation, agitation, confusion	Probably additive effects only	Possible 1+1+1+1+0+0+0+0 +1+0+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 11 β -dehydrogenase, 5 α -reductase, and 5 β -reductase. Glycyrrhizin is metabolized largely to glycyrrhetic acid (an even more potent inhibitor of 5 α -, 5 β -reductase and 11 β -dehydrogenase). Licorice 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 \times 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 IC₅₀s of 2.4, 4.5, and 0.9 $\mu\text{g ml}^{-1}$, 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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