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Review

Herb-drug interactions

Adriane Fugh-Berman

Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. Plausible cases of herb-drug interactions include: bleeding when warfarin is combined with ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), dong quai (*Angelica sinensis*), or danshen (*Salvia miltiorrhiza*); mild serotonin syndrome in patients who mix St John's wort (*Hypericum perforatum*) with serotonin-reuptake inhibitors; decreased bioavailability of digoxin, theophylline, cyclosporin, and phenprocoumon when these drugs are combined with St John's wort; induction of mania in depressed patients who mix antidepressants and *Panax ginseng*; exacerbation of extrapyramidal effects with neuroleptic drugs and betel nut (*Areca catechu*); increased risk of hypertension when tricyclic antidepressants are combined with yohimbine (*Pausinystalia yohimbe*); potentiation of oral and topical corticosteroids by liquorice (*Glycyrrhiza glabra*); decreased blood concentrations of prednisolone when taken with the Chinese herbal product xaio chai hu tang (sho-saiko-to); and decreased concentrations of phenytoin when combined with the Ayurvedic syrup shankhapushpi. Anthranoid-containing plants (including senna [*Cassia senna*] and cascara [*Rhamnus purshiana*]) and soluble fibres (including guar gum and psyllium) can decrease the absorption of drugs. Many reports of herb-drug interactions are sketchy and lack laboratory analysis of suspect preparations. Health-care practitioners should caution patients against mixing herbs and pharmaceutical drugs.

> "Poisons and medicines are oftentimes the same substances given with different intents."
>
> Peter Mere Latham (1789–1875)

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications—eg, herbs traditionally used to decrease glucose concentrations in diabetes[1] could theoretically precipitate hypoglycaemia if taken in combination with conventional drugs.

Herbal medicines are ubiquitous: the dearth of reports of adverse events and interactions probably reflects a combination of under-reporting and the benign nature of most herbs used. Experimental data in the field of herb-drug interactions are limited, case reports scarce, and case series rare. This lack of data is also true of drug-drug interactions: published clinical studies are mainly case reports (controlled trials are scarce, since the random assignment of patients to trials that examine unintended effects is not ethical). The true prevalence of drug interactions is substantial but unknown. One study of 1000 elderly people admitted to a hospital from the emergency department found that 538 patients were exposed to 1087 drug-drug interactions; 30 patients experienced adverse effects as a consequence of these interactions.[2] In clinical practice, polypharmacy is common, and to the mixture physicians prescribe, patients add various over-the-counter medications, vitamins, herbs, and foods. All ingested substances have the potential to interact.

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Source and extent of review

Sources for this review include MEDLINE 1966–98 (searched under MeSH terms "drug interactions" combined with "herbal medicine", "traditional medicine", "Chinese traditional medicine", "African traditional medicine", "Ayurvedic medicine", "Oriental traditional medicine", "Unani medicine", and "Arabic medicine"); EMBASE 1994–99 (searched under the same terms); reference dredging; and my own files on the subject.

Many reports of herb-induced interactions lack crucial documentation on temporal relations and concomitant drug use. Perhaps the most serious problem encountered in analysing such reports is the consistent absence of any effort (beyond that of reading the label) to establish a positive identification of the herb involved, and to exclude the effect of contaminants or adulterants. Unless noted otherwise, the reports mentioned herein did not include chemical analyses.

This review was limited to the most commonly used medicinal plants, and to clinical reports (animal studies

Herb and drug(s)	Results of interaction	Comments
Betel nut (*Areca catechu*)		
Flupenthixol and procyclidine	Rigidity, bradykinesia, jaw tremor[5]	Betal contains arecoline, a cholinergic alkaloid.
Fluphenazine	Tremor, stiffness, akithesia[5]	
Prednisone and salbutamol	Inadequate control of asthma	Arecoline challenge caused dose-related bronchoconstriction in six asthma patients.[6]
Chilli pepper (*Capsicum* spp)		
ACE inhibitor	Cough[7]	Capsaicin depletes substance P.
Theophylline	Increased absorption and bioavailability[8]	
Danshen (*Salvia miltiorrhiza*)		
Warfarin	Increased INR, prolonged PT/PTT[9–11]	In rats, danshen decreases elimination of warfarin.[12] Danshen is in at least one brand of cigarettes.[13]
Devil's claw (*Harpagophytum procumbens*)		
Warfarin	Purpura[14]	
Dong quai (*Angelica sinensis*)		
Warfarin	Increased INR[15,16] and widespread bruising[16]	Dong quai contains coumarins.
Eleuthero or Siberian ginseng (*Eleutherococcus senticocus*)		
Digoxin	Raised digoxin concentrations[17]	Herb probably interfered with digoxin assay (patient had unchanged ECG despite digoxin concentration of 5·2 nmol/L).
Garlic (*Allium sativum*)		
Warfarin	Increased INR[18]	Postoperative bleeding,[19,20] and spontaneous spinal epidural haematoma[21] have been reported with garlic alone. Whether garlic prolongs PT is unclear, but it does cause platelet dysfunction.
Ginkgo (*Ginkgo biloba*)		
Aspirin	Spontaneous hyphema[22]	Ginkgolides are potent inhibitors of PAF.[23,24]
Paracetamol and ergotamine/caffeine	Bilateral subdural haematoma[25]	May not be interaction but due to ginkgo alone. Subarachnoid haemorrhage[26] and subdural haematoma[27] have been reported with the use of ginkgo alone.
Warfarin	Intracerebral haemorrhage[28]	
Thiazide diuretic	Hypertension[18]	This effect may be an unusual adverse reaction to the drug or herb; ginkgo alone has not been associated with hypertension.
Ginseng (*Panax* spp)		
Warfarin	Decreased INR[29]	In rats, concomitantly administered ginseng had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin.[30]
Phenelzine	Headache and tremor,[31] mania[32]	Patient with mania also ingested bee pollen, and had previously had unipolar depression.
Alcohol	Increased alcohol clearance[33]	In mice, ginseng increases the activity of alcohol dehydrogenase and aldehyde dehydrogenase.
Guar gum (*Cyamopsis tetragonolobus*)		
Metformin, phenoxymethylpenicillin, glibenclamide	Slows absorption of digoxin, paracetamol, and bumetanide; decreases absorption of metformin, phenoxymethylpenicillin, and some formulations of glibenclamide[18]	Guar gum prolongs gastric retention.

Table 1: **Clinical reports of herb-drug interactions (B–G)**

***Eleutherococcus senticosis* (Siberian ginseng)**

are cited where relevant). In-vitro experiments have been excluded, since extrapolation of in-vitro evidence to clinical effects is difficult. For example, St John's wort inhibits monoamine oxidase in vitro; however, in-vivo experiments have shown no such effects, and there have been no reported cases linking St John's wort with hypertensive crises associated with monoamine-oxidase inhibitors.[3] However, St John's wort inhibits the uptake of serotonin, norepinephrine, and dopamine in vitro only at quite high concentrations (concentration to inhibit uptake by 50% [IC_{50}] 2·4 mg/L, 4·5 mg/L, and 0·9 mg/L, respectively).[4] That anyone could consume enough of this herb to achieve these concentrations in blood is extremely unlikely. Nevertheless, there have been six cases of serotonin syndrome caused by mixing of St John's wort with serotonin-reuptake inhibitors. The tables summarise the interactions identified by the search strategy.[5–55]

Misidentification, adulteration, and contamination

Labelling of herbal products may not accurately reflect their contents, and adverse events or interactions attributed to specific herbs may actually be due to misidentified plants, pharmaceutical drugs, or heavy metals.[56] For example, a "Siberian ginseng" (*Eleutherococcus senticosus*) product implicated in a case of neonatal androgenisation[57] was found on analysis to be an unrelated species, Chinese silk vine (*Periploca sepium*).[58] In Hong Kong, encephalopathy and neuropathy associated with a Chinese herbal preparation purportedly made from the roots of long-dan-cao (*Gentiana rigescens*) turned out to be due to another plant *Podophyllum emodi*.[56] More than 48 cases of renal poisoning attributed to fang-ji (*Stephania tetrandra*) in a weight-loss preparation were actually caused by guang-fang-ji (*Aristolochia fangchi*): aristolochic acid is a known nephrotoxin.[56] The confusion in the latter case seems to have arisen from the similarity of the names in Chinese.

The addition of pharmaceutical drugs to "herbal" products is a particular problem with Chinese patent medicines. Of 2609 samples of traditional Chinese

Herb and drug(s)	Results of interaction	Comments
Karela or bitter melon (*Momordica charantia*)		
Chlorpropamide	Less glycosuria[34]	Karela decreases glucose concentrations in blood.[35]
Liquorice (*Glycyrrhiza glabra*)		
Prednisolone	Glycyrrhizin decreases plasma clearance, increases AUC,[36] increases plasma concentrations prednisolone[37]	11β-dehydrogenase converts endogenous cortisol to cortisone; orally administered glycyrrhizin is metabolised mainly to glycyrrhetinic acid.[36]
Hydrocortisone	Glycyrrhetinic acid potentiates of cutaneous vasoconstrictor response[38]	Glycyrrhetinic acid is a more potent inhibitor of 5α-, 5β-reductase and 11β-dehydrogenase than is glycyrrhizin.[36]
Oral contraceptives	Hypertension, oedema, hypokalaemia[39]	Oral contraceptive use may increase sensitivity to glycyrrhizin acid.[39] Women are reportedly more sensitive than men to adverse effects of liquorice.[40]
Papaya (*Carica papaya*)		
Warfarin	Increased INR[14]	
Psyllium (*Plantago ovata*)		
Lithium	Decreased lithium concentrations[41]	Hydrophilic psyllium may prevent lithium from ionising.
St John's wort (*Hypericum perforatum*)		
Paroxetine	Lethargy/incoherence[42]	
Trazodone	Mild serotonin syndrome[43]	A similar case is described with the use of St John's wort alone.
Sertraline	Mild serotonin syndrome[44]	
Nefazodone	Mild serotonin syndrome[44]	
Theophylline	Decreased theophylline concentrations[45]	
Digoxin	Decreased AUC, decreased peak and trough concentrations[46]	Most, but not all, studies indicate that St John's wort is a potent inhibitor of cytochrome P450 isoenzymes[47]
Phenprocoumon	Decreased AUC[48]	
Cyclosporin	Decreased concentrations in serum[49]	
Combined oral contraceptive (ethinyloestradiol and desogestrel)	Breakthrough bleeding[49]	
Saiboku-to (Asian herbal mixture)		
Prednisolone	Increased prednisolone AUC[50]	Contains all the same herbs as sho-saiko-to, and *Poria cocos*, *Magnolia officinalis*, and *Perillae frutescens*.
Shankhapushpi (Ayurvedic mixed-herb syrup)		
Phenytoin	Decreased phenytoin concentrations, loss of seizure control[51]	In rats, multiple coadministered doses (but not single doses) decreased plasma phenytoin concentrations; single doses decreased the antiepileptic effect of phenytoin.[51] Shankhapushpi is used to treat seizures.
Sho-saiko-to or xiao chai hu tang (Asian herb mixture)		
Prednisolone	Decreased AUC for prednisolone[50]	Contains liquorice (*Glycyrrhiza glabra*), *Bupleurum falcatum, Pinellia ternata, Scutellaria baicalensis, Zizyphus vulgaris, Panax ginseng,* and *Zingiber officinale.*
Tamarind (*Tamarindus indica*)		
Aspirin	Increased bioavailability of aspirin[52]	Tamarind is used as a food and a medicine.
Valerian (*Valeriana officinalis*)		
Alcohol	A mixture of valepotriates reduces adverse effect of alcohol on concentration[53]	
Yohimbine (*Pausinystalia yohimbe*)		
Tricyclic antidepressants	Hypertension[54]	Yohimbine alone can cause hypertension, but lower doses cause hypertension when combined with tricyclic antidepressants. Effect is stronger in hypertensive than normotensive individuals.[55]

ACE=angiotensin-converting enzyme; INR=international normalised ratio; PT=prothrombin time; PTT=partial thromboplastin time; ECG=electrocardiogram; PAF=platelet-activating factor; AUC=area under the concentration/time curve.

Table 2: **Clinical reports of herb-drug interactions (K–Y)**

medicines collected from eight hospitals in Taiwan, 23·7% contained pharmaceutical adulterants, most commonly caffeine, paracetamol, indomethacin, hydrochlorothiazide, and prednisolone.[59] Non-steroidal anti-inflammatory drugs and benzodiazepines have been found in many Chinese patent medicines sold outside Asia; these compounds include Miracle Herb, Tung Shueh, and Chuifong Toukuwan.[60] The latter preparation is notorious: at different times since 1974, the formulation has contained aminopyrine, phenylbutazone, indomethacin, hydrochlorothiazide, chlordiazepoxide, diazepam, corticosteroids, diclofenac, mefenamic acid, and dexamethasone.[61]

Ginkgo biloba

Heavy-metal contamination is not uncommon in Asian herbal products. 24 of 251 Asian patent medicines collected from herbal stores in California, USA, contained lead (at least 1 ppm); 36 products contained arsenic, and 35 contained mercury.[62]

Counselling of patients about herb-drug interactions

Use of herbal and dietary supplements is extremely common: in one US survey of adults who regularly take prescription medication, 18·4% reported the concurrent use of at least one herbal product or high-dose vitamin (and 61·5% of those who used unconventional therapies did not disclose such use to their physicians).[63] A survey

Panax ginseng

of 515 users of herbal remedies in the UK found that 26% would consult their general practitioner for a serious adverse drug reaction associated with a conventional over-the-counter medicine, but not for a similar reaction to a herbal remedy.[64]

Patients may not be forthcoming about the use of herbal medicine—even if it causes severe adverse effects—because they fear censure. Clinicians must ask patients about their use of herbs in a non-judgmental, relaxed way: a disapproving manner will ensure only that a patient will conceal further use. The patient should be treated as a partner in watching out for adverse reactions or interactions, and should be told about the lack of information on interactions and the need for open communication about the use of herbal remedies. Formulation, brand, dose, and reason for use of herbs should be documented on the patient's charts and updated regularly.

Any laxative or bulk-forming agents will speed intestinal transit, and thus may interfere with the absorption of almost any intestinally absorbed drug.[65] The most popular stimulant laxative herbs are the anthranoid-containing senna (*Cassia senna* and *C angustifolia*) and cascara sagrada (*Rhamnus purshiana*). Dried exudate from the aloe vera (*Aloe barbadensis*) leaf (not gel) also contains anthranoids and is used as a laxative. Aloe vera gel, found within the leaves, is used topically for burns and cuts, and is sometimes recommended by herbalists for internal ingestion to treat ulcers and other disorders. The gel (or juice made from the gel) does not contain anthranoids, but some oral preparations are contaminated by the laxative leaf. Less commonly used anthranoid-containing plants are frangula (*Rhamnus frangula*), yellow dock (*Rumex crispus*), and Chinese rhubarb (*Rheum officinale*).

Patients with clotting disorders, those awaiting surgery, or those on anticoagulant therapy should be warned against the concurrent use of ginkgo, danshen, dong quai, papaya, or garlic. Although the combined use of anticoagulants with these herbs should be discouraged, patients who insist on the combination should have their bleeding times monitored (most of these herbs interfere with platelet function, not the coagulation cascade, and thus will not affect prothrombin time, partial thromboplastin time, or international normalised ratio [INR]). Many other herbs also contain anticoagulant substances; as a precaution, patients on warfarin should have an INR measurement within a week of starting any herbal treatment.

Valeriana officinalis

Patients on serotonin-reuptake inhibitors, cyclosporin, digoxin, phenprocoumon, or any critical chronic medication should avoid St John's wort; those on phenelzine should avoid ginseng; and those on tricyclic antidepressants should avoid yohimbine. Patients taking phenytoin should avoid Ayurvedic herbal mixtures for seizures. Liquorice (a very common ingredient in Chinese herb mixtures) may potentiate the action of corticosteroids, and betel nuts have pronounced cholinergic effects. There are doubtless many as yet undiscovered interactions.

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