Potential Herb-Drug Interactions for Commonly Used Herbs*

How to Read the Chart

The chart is read from left to right. The information in the Basis of Concern column provides the evidence for the information in the Potential Interaction column. For example, *clinical studies* found that administration of St John's wort resulted in *decreased levels* of cancer chemotherapeutic drugs. (Italicized words represent the information in the Herb-Drug Interaction chart below.)

More details may be provided in the Basis of Concern column. For example, in a *clinical study with healthy volunteers* administration of St John's wort resulted in *increased clearance* of the hypoglycemic drug gliclazide, and so *may reduce the drug's efficacy*, however, *glucose and insulin response to glucose loading were unchanged*.

A recommended action is suggested on a risk assessment of the information in the Basis of Concern. In these examples:

- It is recommended that St John's wort is contraindicated in patients taking cancer chemotherapeutic drugs.
- In the case of gliclazide, because the trial found little effect on a clinically-relevant outcome, the potential interaction is considered low risk and a caution is recommended: the patient should be monitored, through the normal process of repeat consultations.

For more information on the process used to assess the herb-drug interaction research (and why some research is not included), how the risk of interaction is assessed, with worked examples from the chart: go to **www.mediherb.com** and view the Herb-Drug Interaction Chart under 'Resources'.

Health care professionals please note: when a patient presents using any of the drugs listed below and there is a potential interaction with the herb you intend to dispense, it is important that you or your patient discuss the potential interaction with their prescribing physician before you dispense the herb to the patient.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Bilberry *Vaccinium myrtillus*			
Warfarin	Potentiation of bleeding.	Herb Alone Antiplatelet activity observed in healthy volunteers (173 mg/day of bilberry anthocyanins).[1] Case report of postoperative bleeding (bilberry extract undefined).[2] Herb or Constituent and Drug Uncontrolled trial (600 mg/day of bilberry anthocyanins + 30 mg/day of vitamin C for 2 months then reduced maintenance dose) of 9 patients taking anticoagulant drugs – treatment reduced retinal hemorrhages without impairing coagulation.[3] Case report (patient reported to consume "large amounts of bilberry fruits every day for five years").[4]	**Monitor** at high doses (> 100 mg/day anthocyanins, low level of risk).
Black Cohosh *Actaea racemosa (Cimicifuga racemosa)*			
Statin drugs eg atorvastatin	May potentiate increase in liver enzymes, specifically ALT.	Case report.[5]	**Monitor** (low level of risk).
Bladderwrack *Fucus vesiculosus*			
Hyperthyroid medication eg carbimazole	May decrease effectiveness of drug due to natural iodine content.[6]	Theoretical concern, no cases reported.	**Contraindicated** unless under close supervision.
Thyroid replacement therapies eg thyroxine	May add to effect of drug.	Theoretical concern linked to a case report where "kelp" caused hyperthyroidism in a person not taking thyroxine.[7]	**Monitor** (low level of risk).
Bugleweed *Lycopus virginicus, Lycopus europaeus*			
Radioactive iodine	May interfere with administration of diagnostic procedures using radioactive isotopes.[8]	Case report.	**Contraindicated**.
Thyroid hormones	Should not be administered concurrently with preparations containing thyroid hormone.[9]	Theoretical concern based on deliberations of German Commission E.	**Contraindicated**.
Cat's Claw *Uncaria tomentosa*			
HIV protease inhibitors	May increase drug level.	Case report, in a patient with cirrhosis being evaluated for a liver transplant.[10]	**Monitor** (low level of risk).
Cayenne (Chili Pepper) *Capsicum* spp. (See also Polyphenol-containing herbs)			
ACE inhibitor	May cause drug-induced cough.	Case report (topical capsaicin). Theoretical concern since capsaicin depletes substance P.[11]	**Monitor** (very low level of risk).
Theophylline	May increase absorption and drug level.	Clinical study (healthy volunteers, chili-spiced meal). Absorption and drug level lower than during fasting.[12]	**Monitor** (low level of risk).

Drug	Potential Interaction	Basis of Concern	Recommended Action
Celery Seed *Apium graveolens*			
Thyroxine	May reduce serum levels of thyroxine.	Case reports.[13]	**Monitor** (very low level of risk).
Chinese Skullcap *Scutellaria baicalensis*			
Losartan	May increase drug levels.	Clinical trial with healthy volunteers (water-based extract,[A] dried herb equivalent: 12 g/day).[14]	**Monitor** (low level of risk at typical doses).
Rosuvastatin	May decrease drug levels.	Clinical study with healthy volunteers using 150 mg/day of isolated constituent (baicalin).[15]	**Monitor** (low level of risk).[B]
Coleus *Coleus forskohlii*			
Antiplatelet and anticoagulant drugs	May alter response to drug.	Theoretical concern initially based on *in vitro* antiplatelet activity of active constituent forskolin, and *in vivo* antiplatelet activity in an animal model (oral doses: standardized Coleus extract and forskolin).[16] More recent *in vivo* animal research: standardized Coleus extract reduced the anticoagulant activity of warfarin.[17]	**Monitor** (low level of risk).
Hypotensive medication	May potentiate effects of drug.	Theoretical concern based on ability of high doses of forskolin and standardized Coleus extract to lower blood pressure in normotensive and hypertensive animals.[18,19] Clinical data from weight management trials: no effect on blood pressure in three trials, trend toward lower blood pressure in one small study.[20,21] No experimental or clinical studies conducted with hypotensive medication.	**Monitor** (low level of risk).
Prescribed medication	May potentiate effects of drug.	Theoretical concern based on ability of forskolin to activate increased intracellular cyclic AMP *in vitro*.[22]	**Monitor** (low level of risk).
Cranberry *Vaccinium macrocarpon*			
Midazolam	May increase drug levels.	Clinical trials with healthy volunteers: effect on drug levels conflicting – increased (double-strength juice[C], 240 mL tds; defined as a weak interaction[D])[23] and no effect (cranberry juice,[E] 200 mL tds).[24]	**Monitor** (low level of risk).
Simvastatin	May increase side effects of drug.	Case report (355–473 mL/day cranberry juice drink (7% juice), rated as 'possible' interaction).[25]	**Monitor** (low level of risk).
Warfarin	May alter INR (most frequently increase).	Case reports (where reported the dosage was often high: up to 2000 mL/day, juice strength undefined; 1.5–2 quarts (1420–1893 mL)/day of cranberry juice cocktail; 113 g/day, cranberry sauce).[26-34] Clinical trials: no significant effect found in atrial fibrillation patients (250 mL/day cranberry juice cocktail),[35] in patients on warfarin for a variety of indications (8 oz (236 mL)/day cranberry juice cocktail),[36] but increase observed in healthy volunteers (juice concentrate equivalent to 57 g of dry fruit/day).[37] No alteration of prothrombin time in patients on stable warfarin therapy (480 mL/day cranberry juice)[38] or of thromboplastin time in healthy volunteers (600 mL/day cranberry juice[E]).[24] *See also note C.*	**Monitor** (low level of risk at typical doses).
Dong Quai *Angelica sinensis, Angelica polymorpha*			
Warfarin	May potentiate effect of drug.	Case reports: increased INR and PT;[39] increased INR and widespread bruising.[40]	**Monitor** (low level of risk).
Echinacea *Echinacea angustifolia, Echinacea purpurea*			
Antiretroviral drugs	HIV non-nucleoside transcriptase inhibitors eg etravirine: May alter drug levels.	Clinical trial (*E. purpurea* root; HIV-infected patients): no effect overall, but large interindividual variability occurred (from near 25% decreases to up to 50% increases in drug concentrations). All maintained an undetectable viral load.[41]	**Monitor** (low level of risk).
	HIV protease inhibitors eg darunavir: May decrease drug levels.	Clinical trial (*E. purpurea root*; HIV-infected patients): no effect overall, but some patients showed a decrease by as much as 40%. All maintained an undetectable viral load. (Patients were also taking a low dose of ritonavir.)[42]	**Monitor** (low level of risk).
Immunosuppressant medication	May decrease effectiveness of drug.[43,44]	Theoretical concern based on immune-enhancing activity of Echinacea. No cases reported.	**Contraindicated**.
Midazolam	Decreases drug levels when drug administered intravenously.[F]	Clinical study (*E. purpurea* root, 1.6 g/day).[45]	**Monitor** (medium level of risk) when drug administered intravenously.
Eleuthero (Siberian Ginseng) *Eleutherococcus senticosus*			
Digoxin	May increase plasma drug levels.	Case report: apparent increase in plasma level, but herb probably interfered with digoxin assay[G] (patient had unchanged ECG despite apparent digoxin concentration of 5.2 nmol/L).[46] In a later clinical trial no effect observed on plasma concentration.[47]	**Monitor** (very low level of risk).

Drug	Potential Interaction	Basis of Concern	Recommended Action
Evening Primrose Oil *Oenothera biennis*			
Phenothiazines	May decrease effectiveness of drug.	Reports of worsening epilepsy in schizophrenics. No causal association demonstrated and no effect observed in later trials.[48]	**Monitor** (very low level of risk).
Garlic *Allium sativum* (See also Hypoglycemic herbs)			
Antiplatelet and anticoagulant drugs	Aspirin: May increase bleeding time. Clopidogrel: May potentiate effect of drug. Warfarin: May potentiate effect of drug. Large doses could increase bleeding tendency.	Concern may be overstated, as antiplatelet/anticoagulant drugs are often coadministered eg aspirin and warfarin. Herb Alone Case reports of increased bleeding tendency with high garlic intake. In three of the four cases the bleeding occurred after surgery.[49-52] Anecdotal: garlic taken shortly before testing interferes with platelet aggregation in control subjects.[53] *Single-dose studies, and studies demonstrating a beneficial effect on disordered function, including for example, in atherosclerosis, are excluded.* Clinical studies (3 g/day or less of fresh garlic): inhibited platelet aggregation in three trials† (about 2.4–2.7 g/day, patients and healthy volunteers),[54-56] but no effect on platelet aggregation in one trial† (about 1.8 g/day, patients);[57] decreased serum thromboxane in one trial (3 g/day, healthy volunteers)[58]. † *See note H.* Clinical studies (4.2–5 g/day of fresh garlic, patients and healthy volunteers): no effect on platelet aggregation, fibrinogen level, prothrombin time, whole blood coagulation time.[59-61] Clinical studies (8–10 g/day of fresh garlic, healthy volunteers): inhibited platelet aggregation and increased clotting time.[62,63] Herb and Drug Aspirin: No published studies. Clopidogrel: Garlic tablet ("odorless", dose undefined) added to improve drug therapy, reduced platelet hyperactivity in two patients.[53] Warfarin: Two cases of increased INR and clotting times, very few details (garlic pearls, garlic tablets: dosage undefined).[64] Clinical trial: no effect in healthy volunteers (enteric-coated tablets equivalent to 4 g/day of fresh garlic).[37]	**Monitor** at doses equivalent to ≥ 3 g/day fresh garlic (low level of risk). **Stop taking** at least one week before surgery.
HIV protease inhibitors	Decreases drug level.	Saquinavir: Two clinical studies (garlic extract, standardized for allicin content) with healthy volunteers[65,66] – large variability (in one study,[66] decrease (15%) was not significant). Ritonavir-boosted atazanavir: Case report (6 stir-fried garlic cloves three times per week).[67]	**Monitor** (medium level of risk).
Ginger *Zingiber officinale*			
Antacids	May decrease effectiveness of drug.	Theoretical concern since ginger increases gastric secretory activity *in vivo* (animals).[43]	**Monitor** (low level of risk).
Antiplatelet and anticoagulant drugs	Phenprocoumon: May increase effectiveness of drug.	Case report (dosage undefined): increased INR.[68]	**Monitor** at doses equivalent to < 4 g/day dried ginger (low level of risk).
	Warfarin: Increased risk of spontaneous bleeding.	Concern based on antiplatelet activity and potential to inhibit thromboxane synthetase. Herb Alone Clinical studies: inhibition of platelet aggregation (5 g, divided single dose, dried ginger) in healthy volunteers,[69] and coronary artery disease patients (10 g, single dose, dried ginger),[70] but no effect in healthy volunteers (2 g, single dose, dried ginger),[71] or coronary artery disease patients (4 g/day, dried ginger);[70] inhibition of platelet thromboxane production in healthy volunteers (5 g/day, fresh ginger).[72] Herb and Drug Case report: bleeding (ginger dosage undefined).[73] No pharmacokinetic or pharmacodynamic effect demonstrated in a clinical trial with healthy volunteers (3.6 g/day, dried ginger).[74] Epidemiological study: ginger (as a complementary medicine) was significantly associated with an increased risk of self-reported bleeding in patients taking warfarin.[75] These results should be viewed cautiously (*see note J*).	**Monitor** at doses equivalent to < 4 g/day dried ginger (very low risk). **Contraindicated** unless under close supervision at doses equivalent to > 4 g/day dried ginger.
Nifedipine	May produce a synergistic antiplatelet effect.	Clinical study (1 g/day, dried ginger) in healthy volunteers and hypertensive patients.[76]	**Contraindicated**.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Ginkgo[K] *Ginkgo biloba*			
Anticonvulsant medication eg carbamazepine, sodium valproate	May decrease the effectiveness of drug.	Case reports, two with well-controlled epilepsy,[77] others anecdotal and uncertain.[78-80]	**Monitor** (medium level of risk). Increasing the intake of vitamin B6 may be advisable for patients taking anticonvulsants.[L]
Antiplatelet and anticoagulant drugs	Prolongation of bleeding and/or increased bleeding tendency.	Concern based on antiplatelet activity. Bleeding events associated with Ginkgo alone or in combination with these and other drugs have been reported but a causal relationship was not established conclusively. Although a retrospective population-based study found risk of hemorrhage was associated with elderly patients (65 years or older) who were taking Ginkgo alone.[81] Herb Alone Rare case reports of bleeding.[82-84] Meta-analysis of randomized, placebo-controlled trials (healthy volunteers and patients): results indicate standardized Ginkgo extract does not increase the risk of bleeding.[85] Randomized, 5-year trial (elderly participants; Ginkgo 50:1 extract, 240 mg/day): no significant difference in incidence of hemorrhagic events.[86] Herb and Drug Retrospective population-based study in Taiwan: the relative risk of hemorrhage associated with the use of Ginkgo extract combined with drugs (clopidogrel, cilostazol, ticlopidine, warfarin) was not significant.[81] *See also note M.* Aspirin: Case reports (2, bleeding;[82] one, extensive bruising after a fall – although possibly high Ginkgo dose (400 mg/day, undefined)).[87] Clinical studies: no additional effect on platelet function, platelet aggregation or bleeding time.[88-90] Cilostazol: Clinical studies with healthy volunteers (Ginkgo extract (undefined): single dose 120 mg) – bleeding time prolonged; no change in platelet aggregation or clotting time, and no significant correlation between prolongation of bleeding time and inhibition of platelet aggregation;[91] no effect on pharmacokinetics or bleeding time, the increase in platelet aggregration was not significant (Ginkgo extract (undefined): 160 mg/day).[92] Clopidogrel: Case report (bruising and bleeding). Clinical study with healthy volunteers (Ginkgo extract (undefined): single dose 120 mg) – no effect on platelet aggregation, bleeding times.[91] Ticlopidine: Case report (bleeding).[83] Clinical studies: no significant additional effect on bleeding time or platelet aggregation (Ginkgo 50:1 extract: single dose 80 mg; healthy volunteers),[94] and at the higher dose (120 mg/day) did not affect drug levels;[95] increased inhibitory response of platelets to testing with two agonists (ie antiplatelet effect) for drug and herb compared with drug alone, although effect was small and statistical and clinical signficance is unknown (Ginkgo extract (undefined): 160 mg/day; pilot study of patients who had an acute ischemic stroke or transient ischemic attack).[96] Warfarin: Case report (bleeding).[82] Clinical studies (healthy volunteers and patients): no additional effect on INR, platelet aggregation, coagulation parameters or plasma drug level.[74,97,98]	**Monitor** (low level of risk)
Antipsychotic medication eg haloperidol, olanzapine, clozapine	May potentiate the efficiency of drug in patients with schizophrenia.	Randomized, controlled trials (Ginkgo 50:1 extract: 120–360 mg/day).[99-102]	Prescribe cautiously. **Reduce** drug if necessary in conjunction with prescribing physician.
Antiretroviral drugs	HIV integrase inhibitors eg raltegravir: May alter drug levels	Clinical study with healthy volunteers (Ginkgo 50:1 extract: 240 mg/day) found an increase in plasma levels, due to large interindividual variability, not considered to be of clinical importance. (The drug's pharmacokinetics are known for considerable intra- and interindividual variability.)[103]	**Monitor** (low level of risk)
	HIV non-nucleoside transcriptase inhibitors eg efavirenz: May decrease drug levels.	Case report.[104]	**Monitor** (medium level of risk).
Atorvastatin – *See Statin drugs below*			
Benzodiazepines	May alter drug level.	Alprazolam: Clinical trial in healthy volunteers found no effect (Ginkgo 50:1 extract: 240 mg/day).[105] Diazepam: Clinical trial in healthy volunteers found no effect (Ginkgo 50:1 extract: 240 mg/day).[106] Midazolam: Clinical trials in healthy volunteers found conflicting results on drug levels: increased (defined as a weak interaction[D]; Ginkgo 50:1 extract: 360 mg/day),[107] decreased (Ginkgo 50:1 extract: 240 mg/day)[108] and no effect (Ginkgo 50:1 extract: 240 mg/day).[109]	**Monitor** (low level of risk).

Drug	Potential Interaction	Basis of Concern	Recommended Action
Hypoglycemic drugs	Glipizide: May cause hypoglycemia.	Observation from aborted trial: hypoglycemia occurred in volunteers with normal glucose tolerance within 60 minutes.[110] Ginkgo 50:1 extract was administered as a single dose of 120 mg.[111]	**Monitor** (low level of risk).
	Metformin: May enhance effectiveness of drug.	Clinical trial: elimination half-life was increased at doses of metformin 850 mg, three times a day. Effect not significant at doses to 500 mg, twice a day. Ginkgo 50:1 extract was administered as a single dose of 120 mg.[110]	**Monitor** at doses of metformin > 1 g/day (medium level of risk). **Reduce** drug if necessary in conjunction with prescribing physician.
	Pioglitazone: May increase drug level.	Clinical trial with healthy volunteers (Ginkgo 50:1 extract: 120 mg/day).[112]	**Monitor** (low level of risk).
	Tolbutamide: May decrease effectiveness of drug.	Clinical trials with healthy volunteers: nonsignificant reduction in glucose-lowering effect of drug (Ginkgo 50:1 extract: 360 mg/day);[107] pharmacokinetics not altered (Ginkgo 50:1 extract: 240 and 360 mg/day).[107,109]	**Monitor** (low level of risk).
Nifedipine	May increase drug levels or side effects.	Clinical studies: mixed results found for mean plasma drug level – increase (120 mg/day)[113] and no effect (240 mg/day).[114] However, at the higher dose, maximal plasma drug level and heart rate was increased with adverse drug reactions for participants with highest plasma drug levels (headache, dizziness, hot flashes).[114]	**Monitor** at doses < 240 mg/day (medium level of risk). **Contraindicated** for higher doses.
Omeprazole	May decrease drug levels.	Clinical trials with healthy volunteers found conflicting results on drug levels: decreased (Ginkgo 50:1 extract: 280 mg/day)[115] and no effect (Ginkgo 50:1 extract: 240 mg/day).[109]	**Monitor** (low level of risk).
Statin drugs	May decrease drug levels.	Atorvastatin: Clinical study with healthy volunteers (Ginkgo 50:1 extract: 360 mg/day). No pharmacodynamic effect was observed.[116] Simvastatin: Clinical study with healthy volunteers (Ginkgo 50:1 extract: 240 mg/day) – drug levels decreased, but active metabolite drug levels not affected. Pharmacodynamics (cholesterol lowering) of the drug not significantly affected, although trend towards lowering of LDL-cholesterol efficacy observed.[117]	**Monitor** (low level of risk).
Talinolol	May increase drug levels.	Clinical trial with healthy volunteers.[118]	**Monitor** (low level of risk).
Golden Seal[N] *Hydrastis canadensis*			
Drugs which displace the protein binding of bilirubin eg phenylbutazone	May potentiate effect of drug on displacing bilirubin.	Herb Alone Theoretical concern based on *in vitro* data (displaced bilirubin from albumin) and in animals with high dose of berberine by injection (reduced bilirubin serum protein binding).[119]	**Monitor** (low level of risk).
Midazolam	May increase drug level.	Clinical trial (defined as a weak interaction[D]).[120]	**Monitor** (low level of risk).
Green Tea *Camellia sinensis* (See also Polyphenol-containing herbs and Tannin-containing herbs)			
Boronic acid-based protease inhibitors eg bortezomib	May decrease efficacy of drug.	Theoretical concern based on initial *in vitro* data and in vivo animal study (green tea constituent: EGCG reduced tumor cell death induced by drug).[121] However, a further *in vivo* animal study found EGCG was not antagonistic to the activity of the drug.[122] *See note P.*	**Contraindicated** at high doses (around 600 mg/day EGCG or 1 g/day green tea catechins).[Q] More information required for doses below this level.
Folate	May decrease absorption.	Clinical study with healthy volunteers.[123] Clinical significance unclear, as was a one-day study (ie not ongoing administration), with 50 mg of green tea catechins administered before, during and up to 2 hours after folate (for a total of 250 mg of catechins).	If taken simultaneously, may need to **increase** dose of folate. The effect may be relatively small – more information is required.
Immunosuppressives	May increase drug levels.	Case report (patient was a CYP3A4 poor metabolizer).[124]	**Monitor** (medium level of risk).
Sildenafil	May increase bioavailability of drug.	Clinical study with healthy volunteers (2 g, single dose, green tea powder containing 60 mg catechins). Blood pressure and electrocardiogram were unchanged.[125]	**Monitor** (low level of risk).
Statin drugs eg simvastatin	May increase plasma level and side effect of drug.	One case reported of muscle pain (side effect). Pharmacokinetic evaluation indicated green tea (1 cup) increased the bioavailability of simvastatin in this patient.[126]	**Monitor** (low level of risk).
Sunitinib	May reduce bioavailability of drug.	Case report (effect appeared dose-dependent). Considering the pharmacokinetic data (interaction in mice), the authors recommended avoiding green tea intake or leaving an interval of 4 hours between beverage and drug intake.[127]	**Contraindicated**, unless **taken** at least 4 hours **apart**.
Warfarin	May inhibit effect of drug: decreased INR.	Case report (brewed green tea: 0.5–1 gallon/day).[128]	**Monitor** (very low level of risk).

Drug	Potential Interaction	Basis of Concern	Recommended Action
Hawthorn *Crataegus monogyna, Crataegus laevigata (C. oxyacantha)* (See also Tannin-containing herbs)			
Digoxin	May increase effectiveness of drug.	Clinical studies indicate a (beneficial) synergistic effect.[129,130] Pharmacokinetics not affected in a clinical study (healthy volunteers).[131]	**Monitor** (low level of risk).
Hypotensive drugs	May increase effectiveness of drug.	Controlled trials where drugs known to be taken by all or many heart disease patients: blood pressure decreased significantly (2 trials),[132,133] decreased nonsignificantly (1 trial)[134] and was unchanged (1 trial).[135] Significant decrease in blood pressure observed in diabetics taking hypotensive drugs (1 trial).[136]	**Monitor** (low level of risk).
Hypoglycemic herbs eg *Gymnema sylvestre* (See also Ginkgo, Korean Ginseng, Milk Thistle, St John's Wort)			
Hypoglycemic drugs including insulin	May potentiate hypoglycemic activity of drug.	In uncontrolled trials, high dose, long-term administration of Gymnema extract (equivalent to 10–13 g/day dried leaf) reduced insulin and hypoglycemic drug requirements in diabetics.[137,138] Several trials have found no effect for garlic on blood glucose in type 2 diabetes, although in a double-blind, placebo-controlled trial (using enteric-coated tablets), a reduction in the dosage of oral hypoglycemic drugs was required (these patients had fasting blood glucose above 8.0 mmol/L (144 mg/dL)).[139]	Prescribe cautiously and monitor blood sugar regularly. **Warn** patient about possible hypoglycemic effects. **Reduce** drug if necessary in conjunction with prescribing physician.
Kava *Piper methysticum*			
CNS depressants eg alcohol, barbiturates, benzodiazepines	Potentiation of drug effects.	Theoretical concern based on deliberations of German Commission E[9] and the anxiolytic activity of kava.[43] Two apparent case reports (kava + benzodiazepines (alprazolam, flunitrazepam)).[140,141] Clinical trials with healthy volunteers: no additional side effects observed for kava (extract containing 240 mg/day of kava lactones) + benzodiazepine (bromazepam),[142] and kava (extract containing 210 mg/day of kavalactones) + alcohol.[143] Clinical study with healthy volunteers: no effect on pharmacokinetic parameters of midazolam (extract provided 253 mg/day of kavalactones).[120]	**Monitor** (low level of risk).
L-dopa and other Parkinson's disease treatments	Possible dopamine antagonist effects.	Case reports.[144,145] Although, kava is unlikely to be responsible for central dopaminergic antagonism (experimental model)[146] and kava reduced parkinsonism induced by neuroleptic drugs (observational study, psychiatric patients).[147]	**Contraindicated** unless under close supervision.
Korean Ginseng *Panax ginseng*			
Antihypertensive medications including nifedipine	General: May decrease effectiveness of drug.	Theoretical concern since hypertension is a feature of GAS. Clinical significance unclear.[43] Assessment of 316 hospital patients found Korean ginseng to have a contrary effect only in a very small percentage: blood pressure increase in 5% of hypertensives; increase in 3% and decrease in 2% of normotensives; decrease in 6% of hypotensives.[148] No information on concurrent medications. *Note for clinical trial data below:* Acute, single-dose trials excluded. High doses used in several trials. Herb Alone Clinical trials: no significant effects found in healthy volunteers,[149,150] those with metabolic syndrome,[151] type 2 diabetes[152] or glaucoma,[153] although baseline blood pressure may be a factor.[151] Herb and Drug Clinical trials: *decreased* blood pressure in essential hypertension,[154] and coronary artery disease[155] but no effect in white coat hypertension[154] and essential hypertension.[156]	**Monitor** (very low level of risk).
	Nifedipine: May increase drug levels.	Clinical trial.[113]	**Monitor** (low level of risk).
Antiplatelet and anticoagulant drugs	General: May potentiate effects of drug.	Herb Alone Two epidemiological studies in Korea: long-term intake (3–5 years) prolonged plasma clotting times (APTT),[157,158] and decreased platelet aggregation.[157] (Dosage in Korea is generally high.) Clinical trial (healthy volunteers): inhibited platelet aggregation, but no effect on coagulation (PT, APTT).[159]	**Monitor** (low level of risk).
	Warfarin: May decrease effectiveness of drug.	Herb and Drug One case reported (decreased INR)[160] but clinical significance unclear. No effect demonstrated in three clinical trials (healthy volunteers and patients) for INR, prothrombin time and platelet aggregation.[161-163] Although the design of the trials has been criticized. *See note R*.[164]	**Monitor** (low level of risk).
Cancer chemotherapeutic drugs eg imatinib	May potentiate adverse effect possibly by altered metabolism.	Case report (hepatotoxicity; probable causality).[165]	**Monitor** (low level of risk).
CNS stimulants	May potentiate effects of drug.[43]	Theoretical concern since CNS stimulation is a feature of GAS. Clinical significance unclear.	**Monitor** (low level of risk).
HIV integrase inhibitors eg raltegravir	May potentiate adverse effect possibly by altered metabolism.	Case report (elevated liver enzymes: probable causality, dosage unknown).[166]	**Monitor** (low level of risk).

Drug	Potential Interaction	Basis of Concern	Recommended Action
Hypoglycemic drugs including insulin	May potentiate hypoglycemic activity of drug.[44]	Theoretical concern based on clinically observed hypoglycemic activity of ginseng in newly diagnosed type 2 diabetics.[167] Clinical significance unclear. No effect on insulin sensitivity or beta-cell function after very high doses in newly diagnosed type 2 diabetics or those with impaired glucose tolerance.[168] Korean red ginseng (2.7 g/day) reduced the requirement for insulin in about 40% of diabetics in a small uncontrolled trial.[169] No adverse effects in three trials of type 2 diabetics well controlled with diet and/or oral hypoglycemic drugs.[152,170,171]	**Monitor** (low level of risk).
MAO inhibitors eg phenelzine	May cause side effects such as headache, sleeplessness, tremor.	Case reports.[172-174]	**Contraindicated**.
Midazolam	May decrease drug level.	Clinical study with healthy volunteers (extract providing about 45 mg/day of ginsenosides).[175]	**Monitor** (low level of risk).
Sildenafil	Potentiation of drug possible.	Theoretical concern based on *in vitro* studies which show ginseng increases nitric oxide release from corpus cavernosum tissue.[176,177]	**Monitor** (very low level of risk).
Laxative (anthraquinone-containing) herbs eg cascara (*Frangula purshiana, Rhamnus purshianus*), yellow dock (*Rumex crispus*)			
Antiarrhythmic agents	May affect activity if potassium deficiency resulting from long-term laxative abuse is present.	German Commission E and ESCOP recommendation.[9,178]	**Avoid** excessive doses of laxatives. Maintain patients on a high potassium diet.
Cardiac glycosides	May potentiate activity, if potassium deficiency resulting from long-term laxative abuse is present.	German Commission E and ESCOP recommendation.[9,178]	**Monitor** (low level of risk at normal doses).
Potassium-depleting agents eg thiazide diuretics, corticosteroids, licorice root (*Glycyrrhiza glabra*)	May increase potassium depletion.	German Commission E and ESCOP recommendation.[9,178]	**Avoid** excessive doses of laxatives. Maintain patients on a high potassium diet.

Herb-Drug Interaction Chart: General Prescribing Guidelines

- Exercise great caution when prescribing herbs for patients taking drugs with a narrow therapeutic window. These drugs may become dangerously toxic or ineffective with only relatively small changes in their blood concentrations. Examples include digoxin, warfarin, antirejection (immunosuppressive) drugs, many anti-HIV drugs, theophylline, phenytoin and phenobarbital. These patients need to be monitored on a frequent, regular basis.
- Exercise great caution when prescribing herbs for patients taking drugs:
  - if heart, liver, or kidney function is impaired,
  - in elderly patients,
  - in pregnant women,
  - in those who have received an organ transplant,
  - in those with a genetic disorder that disturbs normal biochemical functions.

  These patients need to be monitored on a frequent, regular basis.
- Care should be exercised with patients who exhibit long-term use of laxative herbs or potassium-losing diuretics.
- Critical drugs should be taken at different times of the day from herbs (and food) to reduce chemical or pharmacokinetic interactions. They should be separated by at least 1 hour, preferably more.
- Stop all herbs approximately 1 week before surgery. MIlk thistle may help reduce the toxic after-effects of anesthetic drugs, so it can be taken up to the day before, and then again, after surgery.
- Carefully monitor the effects of drugs such as antihypertensives and antidiabetic drugs when combining with herbal remedies. The herbs may make them more or less effective. In the ideal situation the dose of the drug could be adjusted.
- Interactions may be dose related for the herb and the drug, for example, St John's wort and digoxin.

Reference and further reading: Mills S, Bone K (eds). *The Essential Guide to Herbal Safety*. Churchill Livingstone, USA, 2005.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Licorice *Glycyrrhiza glabra*			
Antihypertensive medications other than diuretics	General: May decrease effectiveness of drug.	When consumed in high doses, licorice can cause pseudoaldosteronism and high blood pressure. Herb or Constituent Alone Hypertension demonstrated in case reports, usually from long-term intake and/or very high dose.[179] Hypokalemic paralysis reported (184 mg/day of glycyrrhizin for 2 months), although hypertension was mild, possibly due to coexisting sodium wasting related to uropathy from prostate cancer.[180] Clinical studies (up to 200 g/day of licorice): dose-dependent relationship found between licorice and increase in blood pressure, more pronounced effect in hypertensive patients than in normotensive volunteers, adverse effect greater in women, and effect shown for dose as low as 50 g/day of licorice (75 mg/day of glycyrrhetinic acid = 130 mg/day of glycyrrhizin[S]) taken for 2 weeks.[181-183] Other studies show variation of effects on blood pressure (*see note T*) – renal function may be a factor.[184] The increase in blood pressure after taking glycyrrhetinic acid (874 mg/day of glycyrrhizin) was more pronounced in salt-sensitive than salt-resistant volunteers.[185] Clinical study to establish a no-effect level for glycyrrhizin (healthy female volunteers): significant results (eg blood pressure, serum potassium and aldosterone) compared to controls found for daily dose of 4 mg/kg (220–332 mg/day) taken for 8 weeks, but no effect at lower doses of 1–2 mg/kg (55–166 mg/day) of glycyrrhizin.[186] Herb and Drug Case reports (licorice tea, 3 L/day; patient still hypertensive despite treatment with drugs;[187] decoction of Chinese herbs containing 5 g licorice, taken for 14 days).[188]	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[U] Place patients on a high potassium diet.
	ACE-inhibitor: May mask the development of pseudoaldosteronism.	Case report (patient consumed licorice herbal medicine (200–240 mg/day glycyrrhizin)). Drug dosage was reduced, leading to pseudoaldosteronism.[189] *See note V*.	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[U] Place patients on a high potassium diet.
Cilostazol	May cause hypokalemia, which can potentiate the toxicity of the drug.	Case report (patient taking 150 mg/day of glycyrrhizin). Serum potassium levels were stable prior to administration of drug.[190]	**Monitor** (medium level of risk). Place patients on a high potassium diet.
Corticosteroids	Cortisol: May potentiate the action (rather than increase level of drug).	Inhibition of the enzyme 11beta-HSD2 by glycyrrhizin leads to an increased level of cortisol in the kidney. This does not happen in the liver. The plasma half-life of cortisol may be prolonged when herb and drug are coadministered, but drug concentrations remain normal, possibly because of a concomitant fall in cortisol production.[191] Prolonged half-life of cortisol may suggest the potential for licorice to prolong clearance (and hence, activity) of the drug. (Studies involving patients with Addison's disease or on hemodialysis are not listed here.) Herb or Constituent Alone Clinical studies with healthy volunteers[182,184,192-198] and patients with essential hypertension[182] (ongoing oral administration): increase in urinary excretion of cortisol, but no significant change in plasma cortisol[182,184,192-198] (although plasma cortisone decreased)[192,193,199] and diurnal variation of plasma cortisol was unaffected.[195] Dosage was high: 100–200 g/day of licorice candy (containing glycyrrhizin or glycyrrhetinic acid equivalent to 262–2440 mg/day of glycyrrhizin[S]),[182,194,195,198] 3.5 g/day of licorice tablets (containing 266 mg/day of glycyrrhizin),[196] 4.8 g/day of licorice extract (containing glycyrrhetinic acid = 587 mg/day of glycyrrhizin),[197] 225 mg/day glycyrrhizin,[192] glycyrrhetinic acid (= 227–874 mg/day glycyrrhizin).[184,193] Clinical study with healthy volunteers and hypertensive patients (single dose, placebo-controlled; oral administration of glycyrrhetinic acid equivalent to 874 mg/day of glycyrrhizin[S]): increased plasma cortisol/cortisone ratio (due mostly to a decrease in plasma cortisone); salivary cortisol increased.[200] Clinical study with healthy volunteers (topical application of a cream containing glycyrrhetinic acid): no effect on plasma cortisol.[201] Herb or Constituent and Drug Clinical studies: increased plasma half-life of cortisol (oral administration of licorice candy (200 g/day, containing 580 mg/day glycyrrhizin) + intravenous cortisol to 7 healthy volunteers;[194] oral administration of glycyrrhetinic acid = 227 mg/day of glycyrrhizin[S] + oral cortisol to 2 volunteers).[202,203] *See also Note W*. *Ex vivo* study (skin samples from healthy volunteers and patients with psoriasis and eczema; glycyrrhetinic acid and drug topically applied): activity of hydrocortisone potentiated by glycyrrhetinic acid.[204]	**Monitor** (very low level of risk at normal doses).
	Prednisolone: May potentiate the action or increase level of drug.	Herbal Constituent and Drug Two clinical studies with healthy volunteers (oral administration of glycyrrhizin or glycyrrhetinic acid;[S] prednisolone administered intravenously): increased drug level[205] and increased prednisolone/prednisone ratio[X] in urine and plasma.[206] Dosage was high: 200 mg/day glycyrrhizin,[205] and 400 mg/day glycyrrhetinic acid (= 700 mg/day glycyrrhizin).[206]	**Monitor** (low level of risk at normal doses) when drug administered intravenously.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Digoxin	May cause hypokalemia which can potentiate the toxicity of the drug.	Herb Alone Hypokalemia demonstrated in case reports and clinical studies, usually from long-term intake and/or very high dose, however effect has been demonstrated in sensitive individuals at low doses (licorice containing 100 mg/day of glycyrrhizin). Side effects would be common at 400 mg/day of glycyrrhizin.[179,207,208] Herb and Drug Case report (patient taking herbal laxative containing licorice (1.2 g/day) and rhubarb (*Rheum* spp., 4.8 g/day)). In addition to digoxin, patient was also taking a potassium-depleting diuretic.[209]	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[U] Place patients on a high potassium diet.
Diuretics	Spironolactone (potassium-sparing diuretic): Reduce side effects of drug.	Clinical study: in women with PCOS addition of licorice extract (containing about 463 mg/day glycyrrhizin) reduced side effects related to the diuretic activity of drug.[210]	**Monitor** (low level of risk at normal doses).
	Thiazide and loop (potassium-depleting) diuretics: The combined effect of licorice and the drug could result in excessive potassium loss.[9]	Herb or Constituent Alone Hypokalemia demonstrated in case reports and clinical studies, usually from long-term intake and/or very high dose,[179,207,208] however effect has been demonstrated in patients for ongoing treatment with herbal medicines containing glycyrrhizin at doses of 80–240 mg/day.[211] Herb and Drug Case reports, usually from long-term intake and/or very high dose,[187,207,212-218] however effect has been demonstrated for ongoing treatment of glycyrrhizin as low as 80 mg/day.[211] Clinical trial (candy containing 40 mg/day of glycyrrhizin): decreased plasma potassium, with 20% of healthy volunteers hypokalemic in the first week.[219]	**Contraindicated** unless under close supervision at doses > 40 mg/day glycyrrhizin.
Immunosuppressives eg sirolimus	May decrease drug clearance.	Population pharmacokinetic study with 112 Chinese adult renal transplant recipients: clearance of sirolimus decreased in those patients with abnormal ALT values who were taking herbal formulations containing glycyrrhizin (route and dosage unknown).[220]	**Monitor** (medium level of risk) in hepatically-impaired patients.
Midazolam	May decrease drug level.	Clinical study with healthy volunteers (potassium salt of glycyrrhizin, equivalent to 287 mg/day of glycyrrhizin).[221]	**Monitor** (low level of risk at normal doses).
Omeprazole	May decrease drug level.	Clinical study with healthy volunteers (potassium salt of glycyrrhizin, equivalent to 287 mg/day of glycyrrhizin).[222]	**Monitor** (low level of risk at normal doses).
Potassium-depleting drugs other than thiazide and loop diuretics eg corticosteroids, stimulant laxatives	May result in excessive potassium loss.	Herb Alone Hypokalemia demonstrated in case reports and clinical studies, usually from candy intake (high dose), however effect has been demonstrated in sensitive individuals at low doses (licorice containing 100 mg/day of glycyrrhizin). Side effects would be common at 400 mg/day of glycyrrhizin.[179,207]	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[U] Place patients on a high potassium diet.
Marshmallow Root *Althaea officinalis*			
Prescribed medication	May slow or reduce absorption of drugs.	Theoretical concern based on absorbent properties of marshmallow root.	**Take** at least 2 hours **away** from medication.
Meadowsweet *Filipendula ulmaria* (See also Tannin-containing herbs)			
Warfarin	May potentiate effects of drug.	Theoretical concern based on *in vivo* animal study demonstrating anticoagulant activity (dosage unavailable).[223]	**Monitor** (very low level of risk).
Milk Thistle[K] *Silybum marianum* (See also Polyphenol-containing herbs)			
Hypoglycemic drugs including insulin	May improve insulin sensitivity.	Controlled trials: improved glycemic control and reduced insulin requirements in patients with type 2 diabetes and cirrhosis (silymarin: 600 mg/day),[224] although insulin requirements unchanged in another trial (silymarin: 200 mg/day);[225] improved glycemic control in diabetics treated with hypoglycemic drugs (silymarin: 200 and 600 mg/day),[226,227] improved blood glucose, blood insulin and insulin resistance in PCOS patients treated with metformin (silymarin: 750 mg/day);[228] but no effect on glucose metabolism in NAFLD patients including those with insulin resistance (silymarin: 280 and 600 mg/day).[229,230]	Prescribe cautiously and monitor blood sugar regularly. **Warn** patient about possible hypoglycemic effects. **Reduce** drug if necessary in conjunction with prescribing physician.
Immunosuppressives eg sirolimus	May decrease drug clearance.	Population pharmacokinetic study with 112 Chinese adult renal transplant recipients: clearance of sirolimus decreased in those patients with abnormal ALT values who were taking silymarin formulations (route and dosage unknown).[220]	**Monitor** (medium level of risk) in hepatically-impaired patients.
Losartan	May reduce efficacy of drug by inhibiting metabolism.	Clinical study (healthy volunteers; clinical significance unclear): inhibited metabolism of drug; the inhibition was greater in those of a particular CYP2C9 genotype (silymarin: 420 mg/day).[231] *See note Y.*	**Monitor** (low level of risk).
Metronidazole	May decrease absorption of drug, by increasing clearance.	Clinical study with healthy volunteers (silymarin: 140 mg/day).[232]	**Monitor** (medium level of risk).
Nifedipine	May delay the absorption rate of drug.	Clinical study with healthy volunteers (silymarin: 280 mg/day), but bioavailability unchanged.[233]	**Monitor** (low level of risk).
Ornidazole	May increase drug levels.	Clinical study with healthy volunteers (silymarin: 140 mg/day).[234]	**Monitor** (medium level of risk).
Talinolol	May increase drug levels.	Clinical study with healthy volunteers (silymarin: 420 mg/day).[235]	**Monitor** (low level of risk).

Drug	Potential Interaction	Basis of Concern	Recommended Action
Phellodendron[N] *Phellodendron amurense*			
Drugs that displace the protein binding of bilirubin eg phenylbutazone	May potentiate effect of drug on displacing bilirubin.	Herb Alone Theoretical concern based on *in vitro* data (displaced bilirubin from albumin) and in animals with high dose of berberine by injection (reduced bilirubin serum protein binding).[119]	**Monitor** (low level of risk).
Polyphenol-containing[Z] **or Flavonoid-containing herbs** especially cayenne (*Capsicum annuum*), chamomile (*Matricaria chamomilla* (*Matricaria recutita*)), green tea (*Camellia sinensis*), lime flowers (*Tilia cordata*), milk thistle (*Silybum marianum*), rosemary (*Rosmarinus officinalis*) (See also Tannin-containing herbs)			
Immunosuppressives eg cyclosporin	Decreases drug levels, due to impaired absorption or increased metabolism.	Three case reports, in transplant patients (2 L/day of herbal tea; 1-1.5 L/day of chamomile tea; 'large quantities' of fruit tea containing hibiscus extract, and a drink containing black tea). Confirmed by rechallenge in one case, but no signs of rejection.[236]	**Monitor** (medium level of risk). Also advisable not to take simultaneously.
Iron	Inhibition of non-heme iron[AA] absorption.	Clinical study (included herb teas (German chamomile, vervain, lime flower, peppermint; all 3 g/300 mL), beverages (e.g. black tea, coffee, cocoa)): effect dependent on polyphenol content (per serving: 20-400 mg).[237] *See also note BB.* Timing of intake may be important. *See also note CC.* Epidemiological study (United States): 1 cup/week of coffee associated with 1% lower serum ferritin in the elderly.[238] Epidemiological study (China): effect for eating chili on serum ferritin in women not significant.[239] Mixed results in other studies (healthy volunteers): rosemary (32.7 mg of polyphenols)[240] and cayenne (high dose: 14.2 g, fresh weight,[DD] containing 25 mg polyphenols)[241] caused inhibition; chamomile[242] and turmeric (2.8 g, fresh weight, containing 50 mg polyphenols)[241] did not. *See also note EE.* Results for green tea have been conflicting: two studies found no effect (healthy volunteers and those with anemia),[243,244] two studies (healthy volunteers) found an effect.[240,245] Drinking green tea (1:100, 1 L/day) lowered serum ferritin in women with low levels of ferritin (< 25 mcg/L) at baseline. No effect in other women or men (vegetarians and omnivores), and no effect on iron status parameters.[246] Two epidemiological studies (French and Japanese populations) found mixed results for serum ferritin and hemoglobin, although risk of iron depletion or anemia was not increased.[247,248] Clinical study (150–300 mg/day EGCG): decreased absorption in healthy women with low iron stores administered together with iron. Results significant only at higher dosage.[249] Concentrated extract of milk thistle reduced iron absorption in hemochromatosis patients.[250]	In anemia and where iron supplementation is required, **do not take simultaneously** with meals or iron supplements.
Saw Palmetto *Serenoa repens*			
Antiplatelet and anticoagulant drugs	May potentiate effect of drug.	Herb Alone Case report (hemorrhage during surgery).[251] Clinical trials: *reduced* intraoperative bleeding from transurethral resection of the prostate procedure with preoperative use of liposterolic extract (2 trials); blood loss not different when compared with drug treatment (1 trial).[252] Herb and Drug Case reports (2): increased INR (warfarin + simvastatin,[253] aspirin + clopidogrel;[254] – in the first case, the interaction may have been due to the vitamin E also present in the preparation;[255] in the second case, six times the usual dose of extract was taken).	**Monitor** (very low level of risk).
Schisandra *Schisandra chinensis*			
Immunosuppressives	May increase drug levels.	Sirolimus: Observations in some liver transplanted recipients. Clinical study: markedly increased drug levels in healthy volunteers[255] given *S. sphenanthera* extract, providing 67.5 mg/day of deoxyschisandrin[FF]. Tacrolimus: Observations in some renal and liver transplanted recipients. Clinical studies: markedly increased drug levels in healthy volunteers[256] and transplant recipients,[257,258] given *S. sphenanthera* extract, providing 67.5 mg/day of deoxyschisandrin[FF].	**Monitor** (low level of risk at normal doses).
Midazolam	May increase drug levels.	Increased drug level (defined as a moderate interaction[D]), increase in sleeping time and increase in mild to moderate adverse effects found in healthy volunteers, given *S. chinensis* extract, providing 22.5 mg/day of deoxyschisandrin[FF].[259]	**Monitor** (medium level of risk at normal doses).
Prescribed medication	May accelerate clearance from the body.	Theoretical concern based on *in vivo* animal studies demonstrating enhanced phase I/II hepatic metabolism.[260,261]	**Monitor** (medium level of risk).
Talinolol	May increase drug levels.	Increased drug level and decreased clearance found in healthy volunteers, given *S. chinensis* extract, providing 33.75 mg/day of deoxyschisandrin[FF].[118]	**Monitor** (low level of risk at normal doses).

Drug	Potential Interaction	Basis of Concern	Recommended Action
Slippery Elm Bark *Ulmus rubra*			
Prescribed medication	May slow or reduce absorption of drugs.	Theoretical concern based on absorbent properties of slippery elm.	**Take** at least 2 hours **away** from medication.
St John's Wort[GG] *Hypericum perforatum* (See also Tannin-containing herbs)			
Amitriptyline	Decreases drug levels.[262]	Clinical study.	**Monitor** (medium level of risk).
Anticonvulsants eg carbamazepine, mephenytoin, phenobarbitone, phenytoin	May decrease drug levels via CYP induction.[263-265]	Theoretical concern. An open clinical trial demonstrated no effect on carbamazepine pharmacokinetics in healthy volunteers.[266] Case report: increase in seizures in patient taking several antiepileptic drugs, two of which are not metabolized by cytochrome P450.[267] Clinical study (healthy volunteers; clinical significance unclear): increased excretion of a mephenytoin metabolite in extensive metabolizers, but not in poor metabolizers.[268] *See note HH.*	**Monitor** (low level of risk).
Antihistamine eg fexofenadine	Decreases drug levels.	Clinical studies.[269,270]	**Monitor** (medium level of risk).
Antiplatelet and anticoagulant drugs	Clopidogrel: May potentiate effects of drug.	Clinical studies: increased responsiveness (decreased platelet aggregation or improved residual platelet reactivity) in hyporesponsive volunteers and patients,[271-274] possibly via the formation of the active metabolite (CYP3A4 activity was increased), thus providing a beneficial effect in these patients. This is a complex situation, with the meaning of clopidogrel resistance/hyporesponsiveness debated.[271,275]	In patients with known clopidogrel resistance: **Monitor** (medium level of risk). In other patients: **Monitor** (risk is unknown).
	Phenprocoumon: Decreases plasma drug levels.	Clinical study.[276]	**Contraindicated**.
	Warfarin: Decreases drug levels and INR.	Case reports (decreased INR (nine cases), increased INR (three cases)).[277-279] Clinical study with healthy volunteers (decreased drug level and INR).[161]	**Contraindicated**.
Benzodiazepines	Decreases drug levels, and is probably dependent upon the hyperforin content.[280]	Alprazolam: Mixed results for drug levels in two clinical studies (similarly low amount of hyperforin, ~4 mg/day) – no effect (dried herb equivalent: 1.1 g/day)[281] and decrease.[282]	**Monitor** (medium level of risk).
		Midazolam: Clinical studies, effect not regarded as clinically relevant for low (< 1 mg/day) hyperforin extracts.[270,280,283,284]	Hyperforin-rich extracts: **Monitor** (medium level of risk). Low-hyperforin extracts: **Monitor** (low level of risk).
		Quazepam: Decreased drug levels, but no effect on pharmacodynamics (sedation).[285]	**Monitor** (low level of risk).
Calcium channel antagonists	Decreases drug levels.	Nifedipine: Clinical studies.[113,286]	**Contraindicated**.
		Verapamil: Clinical study.[287]	**Contraindicated**.
Cancer chemotherapeutic drugs eg irinotecan, imatinib	Decreases drug levels.	Clinical studies.[288-291]	**Contraindicated**.
Clozapine	Decreases drug levels.	Case report.[292]	**Contraindicated**.
Digoxin	Decreases drug levels.	Clinical studies (several studies showed decrease, one study showed no effect)[281,293-295] but effect is dependent upon dose of herb and the hyperforin content.[295]	**Contraindicated** at doses equivalent to > 1 g/day dried herb, especially for high-hyperforin extracts.
Docetaxel (intravenous)	May decrease effectiveness of drug.	Clinical study with cancer patients:[296] effect on pharmacokinetics probably not clinically relevant (eg plasma levels decreased by only 6%); drug-induced side effects were also reduced. *See also Note JJ.*	**Contraindicated**.
Finasteride	May decrease drug levels.	Clinical study with healthy volunteers.[297] Case report: PSA level elevated (due to decreased efficacy of drug?) in patient with benign prostatic hyperplasia.[298]	**Contraindicated**.
HIV non-nucleoside transcriptase inhibitors eg nevirapine	Decreases drug levels.	Case report.[299]	**Contraindicated**.
HIV protease inhibitors eg indinavir	Decreases drug levels.	Clinical study.[300]	**Contraindicated**.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Hypoglycemic drugs	Gliclazide: May reduce efficacy of drug by increased clearance.	Clinical study with healthy volunteers, but glucose and insulin response to glucose loading were unchanged.[301]	**Monitor** (low level of risk).
	Repaglinide: May alter metabolism of drug.	Clinical study with healthy volunteers: no effect, and glucose and insulin response to glucose loading were unchanged.[302]	**Monitor** (very low level of risk).
	Tolbutamide: May affect blood glucose.	Two clinical studies (healthy volunteers): no effect on pharmacokinetics,[281,283] but there was an increased incidence of hypoglycemia in the trial using hyperforin-rich extract (33 mg/day).[283]	**Monitor** (low level of risk).
Immunosuppressives	Decreases drug levels.	Cyclosporin: Case reports,[303-311] case series,[312,313] clinical studies.[270,314] Interaction is dependent upon the hyperforin content.[306,316] Tacrolimus: Case report and clinical studies.[315-317]	**Contraindicated** especially for high-hyperforin extracts.
Ivabradine	May decrease drug levels.	Clinical trial with healthy volunteers. No pharmacodynamic effect was observed.[318]	**Monitor** (medium level of risk).
S-Ketamine (oral)	May decrease drug levels.	Clinical study with healthy volunteers. No pharmacodynamic effect was observed (eg analgesic effect not altered).[319]	**Monitor** (medium level of risk).
Methadone	Decreases drug levels, possibly inducing withdrawal symptoms.	Case reports.[320]	**Contraindicated**.
Methylphenidate	May decrease efficacy.	Case report,[321] but clinical significance unclear.	**Monitor** (low level of risk).
Morphine (oral)	May potentiate effects of drug.	Clinical study (healthy volunteers):[322] pain scores were decreased when morphine co-administered with standardized extract at a dose of herb below those used to obtain an antidepressant or analgesic effect. The effect was dependent hypericin content, but not hyperforin. The authors suggest the herb may be able to decrease the dose of morphine while obtaining the same analgesic effect.	**Monitor** (medium level of risk).
Omeprazole	May decrease drug levels.	Clinical trial.[323]	**Monitor** (low level of risk).
Oral contraceptives	May increase metabolism and reduce effectiveness of drug.	Breakthrough bleeding reported which was attributed to increased metabolism of drug.[277,303] Clinical significance unclear. Cases of unwanted pregnancies have been reported.[324-326] Contradictory results for effect on bioavailability, hormone levels and ovulation demonstrated in three clinical studies, although some breakthrough bleeding occurred.[327-329] In one clinical trial an extract low in hyperforin did not affect plasma contraceptive drug levels or cause breakthrough bleeding.[330] Clinical trial: clearance of levonorgestrel at emergency contraceptive doses increased (not statistically significant).[331] Clinical study: antiandrogenic effect of contraceptive not affected.[332]	Hyperforin-rich extracts: **Monitor** (medium level of risk). Low-hyperforin extracts: **Monitor** (very low level of risk).
Oxycodone	Decreases drug levels.	Clinical trial with healthy volunteers.[333]	**Monitor** (medium level of risk).
SSRIs eg paroxetine, trazodone, sertraline **and other serotonergic agents** eg nefazodone, venlafaxine	Potentiation effects possible in regard to serotonin levels.	Case reports: clinical significance unclear.[334-339]	**Monitor** (very low level of risk).
Statin drugs	May decrease effect and/or drug levels.	Atorvastatin: Clinical study, serum LDL-cholesterol increased by 0.32 mmol/L (12.3 mg/dL) which corresponds to a decrease in effect of drug in patients by about 30%. Serum total cholesterol was also increased.[340] Pravastatin: Clinical study, no effect on plasma level in healthy volunteers.[341] Rosuvastatin: Case report.[342] Simvastatin: Two clinical studies, decrease in drug levels in healthy volunteers,[341] and small increases in serum total cholesterol and LDL-cholesterol in patients.[343]	**Monitor** blood cholesterol regularly (medium level of risk).
Talinolol	May decrease drug levels.	Clinical study with healthy volunteers.[344]	**Monitor** (medium level of risk).
Theophylline	May decrease drug levels.	Case report.[345] No effect observed in clinical study.[346]	**Monitor** (low level of risk).
Voriconazole	Decreases drug levels.	Clinical study.[347]	**Monitor** (medium level of risk).
Zolpidem	May decrease drug levels (but with wide interindividual variability).[KK]	Clinical study (healthy volunteers).[348]	**Monitor** (low level of risk).

Drug	Potential Interaction	Basis of Concern	Recommended Action
Tannin-containing or OPC-containing herbs eg grape seed extract (*Vitis vinifera*), green tea (*Camellia sinensis*), hawthorn (*Crataegus* spp.), meadowsweet (*Filipendula ulmaria*), pine bark (*Pinus massoniana*), raspberry leaf (*Rubus idaeus*), sage (*Salvia fruticosa*), St John's wort (*Hypericum perforatum*), uva ursi (*Arctostaphylos uva-ursi*), willow bark (*Salix* spp.) (See also Polyphenol-containing herbs)			
Minerals especially iron	Iron: May reduce absorption of non-heme iron[AA] from food.	Clinical studies in healthy volunteers, administration during or immediately following the meal [237,349-356] (black tea, typical strength: 0.8–3.3 g/100 mL;[237,349-355] sorghum[LL] (0.15% tannins)[354]), and in women with iron deficiency anemia[357] (black tea: 1–2 x 150 mL of 1:100 infusion containing 78 mg of tannins per 150 mL).[357] Iron absorption reduced to a greater extent in those with iron deficiency anemia (IDA).[357] However, the results from single test meals may exaggerate the effect of iron inhibitors and enhancers.[358] Effects were not significant in a 14-day study.[245] Cases of IDA resistant to treatment: heavy black tea drinkers (2 cases, 1.5–2 L/day).[359,360] Epidemiological studies (12, to 2002) found mixed results, but some evidence of an association between drinking black tea and poor iron status.[358] Clinical study in patients with hemochromatosis (black tea: 250 mL with meal).[361]	**Take** at least 2 hours **away** from food or medication.
	Zinc: May reduce absorption from food.	Clinical studies with healthy volunteers: results conflicting for effect on zinc (undefined tea,[362] black tea[245] consumed at or immediately after food).	**Take** at least 2 hours **away** from food or medication.
Turmeric[N] *Curcuma longa*			
Talinolol	May decrease drug levels.	Clinical study with healthy volunteers (300 mg/day of curcuminoids).[363]	**Monitor** at high doses (≥ 300 mg/day curcumin, low level of risk).
Valerian *Valeriana officinalis*			
CNS depressants or alcohol	May potentiate effects of drug.	Theoretical concern expressed by US Pharmacopeial Convention.[364] However a clinical study found no potentiation with alcohol.[365] Case report of adverse effect with benzodiazepine drug (lorazepam)[366] – herb dosage undefined but likely high (tablet contained valerian and passionflower (*Passiflora incarnata*)). Alprazolam: Clinical study in healthy volunteers found no effect on drug levels (extract provided 11 mg/day total valerenic acids).[367]	**Monitor** (very low level of risk).
Willow Bark *Salix alba, Salix daphnoides, Salix purpurea, Salix fragilis* (See also Tannin-containing herbs)			
Warfarin	May potentiate effects of drug.	Herb Alone Clinical study observed very mild but statistically significant antiplatelet activity (extract containing 240 mg/day of salicin).[368]	**Monitor** (low level of risk).

CODE FOR RECOMMENDED ACTION

Contraindicated: Do not prescribe the indicated herb.

Monitor: Can prescribe the indicated herb but maintain close contact and review the patient's status on a regular basis. Note that where the risk is assessed as medium, self-prescription of the herb in conjunction with the drug is not advisable.

ABBREVIATIONS

ACE: angiotensin-converting enzyme; **ALT:** alanine transaminase, also known as glutamic pyruvic transaminase (GPT); **AMP:** adenosine monophosphate; **APTT:** activated partial thromboplastin time; **AUC:** area under the plasma/serum concentration-time curve (measures extent of absorption); **CNS:** central nervous system; **CYP:** cytochrome P450; **ECG:** electrocardiogram/graph; **EGCG:** epigallocatechin gallate; **GAS:** ginseng abuse syndrome; **HIV:** human immunodeficiency virus; **11beta-HSD2:** 11beta-hydroxysteroid dehydrogenase type 2; **IDA:** iron deficiency anemia; **INR:** international normalized ratio; **LDL:** low density lipoprotein; **NAFLD:** nonalcoholic fatty liver disease; **OPC:** oligomeric procyanidin; **PCOS:** polycystic ovary syndrome; **PSA:** prostate specfic antigen; **PT:** prothrombin time; **SSRI:** selective serotonin reuptake inhibitors; **tds:** three times per day; **>:** greater than; **≥:** greater than or equal to; **<:** less than.

Health care professionals please note: when a patient presents using any of the drugs listed and there is a potential interaction with the herb you intend to dispense, it is important that you or your patient discuss the potential interaction with their prescribing physician before you dispense the herb to the patient.

NOTES

* This chart contains information the authors believe to be reliable or which has received considerable attention as potential issues. However, many theoretical concerns expressed by other authors have not been included. Due to the focus on safety, positive interactions between herbs and drugs, and the effect of drugs on the bioavailability of herbs are generally not included.

A. Research paper describes administration of Scutellaria radix. Trial authors confirm this was root of Chinese skullcap (*Scutellaria baicalensis*).[369]

B. Analysis of Chinese skullcap root samples from Japan found the baicalin content varied from 3.5 to 12%. For a dose of
150 mg/day of baicalin, 1.2–4.3 g/day of dried root would be required.[370]

C. Single-strength (freshly squeezed, 100%) cranberry juice is highly acidic and astringent, making it unpalatable. For this reason, cranberry juice is usually diluted and sweetened (often known as cranberry juice drink). Cranberry juice cocktail usually contains 25% cranberry juice, although can be up to 35%. Cranberry juice drinks contain about 10% cranberry juice. Cranberry sauce is about half the strength of cranberry juice cocktail, about the same strength as juice drinks. Cranberry juice can be concentrated to a dry powder (unsweetened and usually up to 25:1) and used in tablets and capsules. Juices can be prepared by diluting juice concentrates yielding a concentrated juice (eg double-strength juice, at twice the strength of single-strength, squeezed juice). It is likely that unless defined, cranberry juice referred to in case reports and clinical studies is juice drink containing around 10% cranberry juice.

D. Refer to Assessment of Risk & Recommended Action (available on www.mediherb.com) for definition of the extent of this interaction.

E. The cranberry 'juice' administered was similar in concentration to a reference cranberry 'juice' containing about 25% cranberry juice,[371] but with a higher concentration of anthocyanins, and lower in catechins and organic acids. *See also note C.*

F. No effect overall when midazolam was administered orally: oral clearance and area under the drug concentration-time curve were unchanged.

G. Eleutherosides (from Eleuthero) and ginsenosides (from Korean ginseng) have some structural similarity with digoxin. Because of this similarity interference with serum digoxin measurements is possible, as confirmed when mice fed these herbs demonstrated digoxin activity in their serum. More specific assays are able to negate the interference.[372]

H. These four trials used tablets containing a concentrated, standardized extract. A dosage of 900 mg/day of dry extract was equivalent to about 2.7 g/day of fresh garlic,[373] and was said to provide 12 mg/day of alliin,[54,62] although there is some doubt as to the amount of allicin released from this brand of tablet from around 1995 to 2000.[374]

J. There may have been variation in patients' interpretations (of bleeding) and the significant association between ginger use and bleeding was based on 7 self-reported events in 25 users.[375]

K. Information is provided for specialized and/or concentrated extract, rather than galenical form of herb.

L. Ginkgotoxin (4'-O-methylpyridoxine) is present in substantial amounts in Ginkgo seed, and convulsions arising from ingestion of Ginkgo seed have been documented in Japan (infants are particularly vulnerable). Ginkgotoxin is known to inhibit vitamin B6 phosphorylation, which may lead to increased neuronal excitability.[376] Poisoning by ginkgotoxin can be counteracted by vitamin B6,[376] in cases of poisoning it is administered by intravenous injection.[377,378] Ginkgotoxin is present in very small amounts in standardized Ginkgo leaf extracts,[379] but is below the detection limits in human plasma after oral doses (240 mg of 50:1 extract, equivalent to 12 g of dried leaf).[380] According to the manufacturer, despite the extensive use of this special extract (more than 150 million daily doses per year for more than two decades) no cases of epileptic seizure have been attributed to this extract.[380] (Ginkgo preparations associated with the above case reports were undefined.) Strictly speaking this is a potential adverse effect (rather than a herb-drug interaction) as there is no pharmacokinetic data indicating an interaction for coadministration of Ginkgo and anticonvulsants in humans. An interaction is suggested though, because Ginkgo has been found to induce CYP2C19 activity (see entry for omeprazole), an enzyme involved in the metabolism of some anticonvulsants.a

M. Analysis of over 320 000 patients in a German adverse drug reaction reporting system (1999-2002) found no increase in prevalence of bleeding during Ginkgo intake compared to periods without Ginkgo in those taking anticoagulant or antiplatelet medication.[381] In a trial involving 3069 healthy volunteers treated for an average of 6.1 years, there were no statistically significant differences between placebo and Ginkgo in the rate of major bleeding or the incidence of bleeding in individuals taking aspirin. (Compliance during the trial was however low (at the end of the trial, about 60% were taking Ginkgo/placebo).)[382] In Korea, Ginkgo extract is administered with ticlopidine for the prevention of ischemic stroke or acute coronary syndrome.[383]

N. Information is provided for herbs containing standard levels of active constituents. See elsewhere for information on extracts containing very high levels of active constituents such as berberine and curcumin.

P. The *in vitro* reduction by EGCG was overcome when the concentration of the drug was increased (to a level expected clinically ie in plasma from the standard drug dose).[384] A further *in vivo* study found no reduction in the activity of the drug (when EGCG administered by injection to achieve plasma levels of 11–16 microM).[122]

Q. The *in vitro* study found a pronounced reduction in the cytotoxic effect of the drug for a concentration of 2.5–5 microM of EGCG, and when applied as green tea polyphenols a very substantial effect occurred at a EGCG concentration of 1 microM (the other polyphenols may contribute to the activity).[121] A pharmacokinetic study with healthy volunteers found a EGCG plasma concentration of 0.7 microM after a dose of 580 mg of EGCG, and a EGCG plasma concentration of 0.5 microM after a dose of 1 g of green tea polyphenols.[385]

R. A better design would have volunteers take warfarin alone for a period long enough to allow the drug to reach its maximum effect (about 3–5 days) before adding the herb.

S. Glycyrrhetinic acid, is the aglycone of glycyrrhizin. Glycyrrhizin, is the glycoside and contains the aglycone (glycyrrhetinic acid) and a sugar unit.

T. No effect on blood pressure in healthy volunteers in two studies (130 mg/day of glycyrrhetinic acid = 227 mg/day of glycyrrhizin, for 14 days;[184] licorice tablets (266 mg/day of glycyrrhizin) for 56 days);[196] including where plasma renin levels were high (3.1 ng/mL/h),[196] but in another study, blood pressure increased in healthy volunteers taking 546 mg/day of glycyrrhizin for 4 weeks, only for those with plasma renin activity greater than 1.5 ng/mL/h.[386]

U. This is a guide, based on a recommendation from the German Commission E for long-term consumption of licorice as a flavoring. Glycyrrhizin is also known as glycyrrhizinic acid and glycyrrhizic acid.

V. ACE-inhibitors cause mild natriuresis (an increase in sodium excretion in the urine) and occasionally hyperkalemia. The mechanism of the interaction is not known, although it may involve opposing effects on 11beta-hydroxysteroid dehydrogenase type 2 (glycyrrhizin inhibiting, ACE-inhibitor promoting), thus affecting mineralocorticoid receptor activity. Reduction of drug dosage revealed the existing hypokalemia caused by this dosage of glycyrrhizin.

W. Maximum plasma cortisol (exogenous) was not increased in one volunteer;[203] in the other, plasma (exogenous) cortisone/cortisol ratio decreased,[202] suggesting increased (exogenous) cortisol while (endogenous) cortisol decreased (although statistical and clinical significance is unknown, and may have been within the normal range). In these studies isotope-labelled cortisol was administered, which allowed exogenous and endogenous cortisol to be measured.

X. A higher prednisolone/prednisone ratio indicates decreased conversion of prednisolone (active) to prednisone (inactive).

Y. Several variants of CYP2C9 have been identified in humans: the most important mutations are CYP2C9*2 and CYP2C9*3. The CYP2C9*3 variant shows decreased metabolic activity for many drugs metabolized by CYP2C9. CYP2C9 is the main enzyme responsible for transforming losartan to its active metabolite.

Z. The word tannin has a long established and extensive usage although it is considered in more recent years to lack precision. Polyphenol is the preferred term when considering the properties at a molecular level. Plant polyphenols are broadly divisible into proanthocyanidins (condensed tannins) and polymers of esters based on gallic and/or hexahydroxydiphenic acid and their derivatives (hydrolyzable tannins).[387] The terms 'tannin' and 'polyphenol' are sometimes used interchangeably. For example, the results of a clinical study are described: "polyphenols present in tea and coffee inhibited iron absorption in a dose-dependent manner". The 'polyphenol' content was measured using a spectrophotometric method for the determination of "tannins and other polyphenolics".[356] Depending on the analytical method used, it is possible that the polyphenol content may actually be the content of tannins or tannins + polyphenols.[388] It is recommended that both sections of this chart be considered: Polyphenol-containing or Flavonoid-containing herbs, and Tannin-containing or OPC-containing herbs.

AA. Heme iron is derived from hemoglobin and myoglobin mainly in meat products. Non-heme iron is derived mainly from cereals, vegetables and fruits.

BB. At an identical concentration of total polyphenols, black tea was more inhibitory than all the herb teas excluding peppermint: black tea was of equal inhibition to peppermint tea.[237] The type of polyphenols present, as well as the concentration, may affect iron absorption.

CC. Another clinical study also found a dose-dependent effect, and the reduced absorption was most marked when coffee was taken with the meal or one hour later. No decrease in iron absorption occurred when coffee was consumed one hour before the meal.[355]

DD. Administered in freeze-dried form (4.2 g), which would be expected to have a lower inhibitory effect than with the use of fresh chili, as freeze drying probably decreased the ascorbic acid content (ascorbic acid enhances iron absorption).[241]

EE. The different results for cayenne and turmeric under the same experimental conditions, suggest it is not only the quantity of polyphenol present that determines the inhibition, but also for example, the structure of the polyphenol (and hence mechanism of iron binding).[241]

FF. Fructus Schisandra is defined as the fruit of *Schisandra chinensis* or *Schisandra sphenanthera* in traditional Chinese medicine. The major constituents are dibenzocyclooctene lignans. Several factors including harvest season, origin of herb and extraction solvent affect the levels of the individual lignans. Aqueous or ethanolic extracts of *S. chinensis* are not likely to contain more than 2.5 mg/g of deoxyschisandrin.[389,390] A maximum dose of *S. chinensis* extract equivalent to 4 g/day, would provide 10 mg/day of deoxyschisandrin.

GG. As noted for several drugs, the hyperforin content of the St John's wort preparation, as well as the dosage of herb, affects the extent of the interaction. All types of preparations can contain hyperforin, including dry extracts used in tablets and capsules. Hyperforin is however, unstable – particularly when in solution.[391] Tinctures and liquid extracts made using a standard ethanol content (45%) contain negligible amounts of hyperforin. Liquid extracts using a higher ethanol content (such as 60%) will contain a higher initial amount of hyperforin than standard liquid extracts. Over time the hyperforin content is substantially reduced and after a few months tinctures and liquid extracts contain no hyperforin.[392]

HH. Genetic polymorphisms are important in determining differences in the response to drugs, and may influence interactions. There are many genetic variants of the CYP genes, including the CYP2C19 gene. Phenotypes of CYP2C19 have been classified functionally as extensive metabolizers and poor metabolizers, the latter having a deficiency of CYP2C19 activity.[222,393]

JJ. Two of the 10 patients with the highest hyperforin levels prior to drug administration showed the greatest decrease in the AUC_{∞} of docetaxel, for the other patients, no apparent correlation between hyperforin levels and the docetaxel AUC_{∞} was observed.

KK. Of the 14 volunteers, in three, a small increase in AUC was observed after administration of St John's wort.

LL. Sorghum also contains phytate. Both phytate and polyphenol inhibit nutrients such as iron.[394,395]

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