MEDI HERB®

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' look for the link to 'Prescribing Guidelines & Assessment of Risk.

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
Andrographis *Andrographis paniculata*			
Immunosuppressant medication	May decrease effectiveness of drug.[1]	Theoretical concern based on immune-enhancing activity of Andrographis.	**Contraindicated**
Midazolam	May potentiate effects of drug.	Clinical study with healthy volunteers (providing 100 mg/day of andrographolide): pulse rate and blood pressure decreased.[2] *See note A.*	**Monitor** (medium level of risk).
Ashwagandha *Withania somnifera*			
Thyroxine	May potentiate effects of drug.	Theoretical concern based on stimulating effect on thyroid hormones. Case report (increased serum T4 level).[3] Clinical study: improved serum T4 level in subclinical hypothyroid patients;[4] three bipolar patients in a clinical trial experienced small increases in serum T4 from baseline (one subclinical hypothyroid patient),[5] although the extract was made from leaf and root and provided a high concentration of withanolides (50 mg/day).[6]	**Monitor** (low level of risk).
Bilberry *Vaccinium myrtillus*			
Warfarin	Potentiation of bleeding.	Herb Alone Antiplatelet activity observed in healthy volunteers (173 mg/day of bilberry anthocyanins).[7] Case report of postoperative bleeding (bilberry extract undefined).[8] 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.[9] Case report (rectal bleeding and hematuria with elevated INR; patient reported to consume "large amounts of bilberry fruits every day for five years").[10]	**Monitor** at high doses (> 100 mg/day anthocyanins, low level of risk).
	May decrease effectiveness of drug.	Case report (decreased INR, 200 mL/day of 'concentrate' juice; causality rated as possible (score 4)[B]).[11]	**Monitor** (low level of risk).
Black Cohosh *Actaea racemosa (Cimicifuga racemosa)*			
Statin drugs eg atorvastatin	May potentiate increase in liver enzymes, specifically ALT.	Case report.[12]	**Monitor** (low level of risk).
Bladderwrack *Fucus vesiculosus*			
Hyperthyroid medication eg carbimazole	May decrease effectiveness of drug.	Theoretical concern due to natural iodine content.	**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.[13]	**Monitor** (low level of risk).

* This chart is up-to-date as of January 2020.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Boswellia *Boswellia serrata*			
Warfarin	May increase effectiveness of drug.	Two case reports (increased INR; concentrated extract (95%; 1.2–1.5 g/day), causality rated as probable (score 6)[8]).[11]	**Monitor** (low level of risk).
Bugleweed *Lycopus virginicus, Lycopus europaeus*			
Radioactive iodine	May interfere with administration of diagnostic procedures using radioactive isotopes.[14]	Case report.	**Contraindicated**.
Thyroid hormones	Should not be administered concurrently with preparations containing thyroid hormone.[15]	Theoretical concern based on deliberations of German Commission E.	**Contraindicated**.
Cat's Claw *Uncaria tomentosa*			
***L*-Dopa** and other Parkinson's disease treatments	May impair absorption and drug levels.	Case report.[16]	**Monitor** (low level of risk).
HIV protease inhibitors	May increase drug level.	Case report, in a patient with cirrhosis being evaluated for liver transplant.[17]	**Monitor** (low level of risk).
Cayenne (Chili Pepper) *Capsicum* spp. (See also Polyphenol-containing and/or Tannin-containing herbs)			
ACE inhibitor	May cause drug-induced cough.	Case report (topical capsaicin). Theoretical concern since capsaicin depletes substance P.[18]	**Monitor** (very low level of risk).
Theophylline	May increase absorption and drug level.	Clinical study (healthy volunteers, chili-spiced meal).[19]	**Monitor** (low level of risk).
Celery Seed *Apium graveolens*			
Thyroxine	May reduce serum levels of thyroxine.	Case reports.[20]	**Monitor** (very low level of risk).
Chaste Tree *Vitex agnus-castus*			
Hormone-related medications eg progesterone drugs, hormonal contraceptive or HRT	May affect hormone levels and/or alter efficacy of hormone-containing medications	Case report of unwanted pregnancy in Australia (herb and concurrent use of progesterone-only OCP) and one other similar case reported internationally.[21] There are several trials published in which the herb has been administered to women using OCP without causing unwanted pregnancy – *see note C.*	**Monitor** (low level of risk).
Chinese Skullcap *Scutellaria baicalensis*			
Rosuvastatin	May decrease drug levels.	Clinical study with healthy volunteers using 150 mg/day of isolated constituent (baicalin).[22]	**Monitor** (low level of risk).[D]
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).[23] More recent *in vivo* animal research: standardized Coleus extract reduced the anticoagulant activity of warfarin.[24]	**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.[25,26] Clinical data from weight management trials: no effect on blood pressure in three trials, trend toward lower blood pressure in one small study.[27,28] Clinical trial (dose-escalation in healthy volunteers; extract providing 25-100 mg/day of forskolin): no significant effect on blood pressure or heart rate.[29]	**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*.[30]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Cranberry *Vaccinium macrocarpon*			
Midazolam	May increase drug levels.	Clinical trials with healthy volunteers: effect on drug levels conflicting – increased (double-strength juice[E], 240 mL tds)[31] and no effect (cranberry juice,[F] 200 mL tds).[32]	**Monitor** (low level of risk).
Statin drugs	May increase side effects of drug.	Two case reports (355–473 mL/day cranberry juice drink (7% juice), and 473 mL/day 'cranberry juice').[33,34]	**Monitor** (low level of risk).
Tacrolimus	May decrease drug levels.	Case report (2 g/day 'juice extracts'; causality rated as possible (score 4)[B]).[35]	**Monitor** (medium 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).[36-44] Clinical trials: no significant effect found in atrial fibrillation patients (250 mL/day cranberry juice cocktail),[45] in patients on warfarin for a variety of indications (8 oz (236 mL)/day cranberry juice cocktail),[46] but increase observed in healthy volunteers (juice concentrate equivalent to 57 g of dry fruit/day).[47] No alteration of prothrombin time in patients on stable warfarin therapy (480 mL/day cranberry juice)[48] or of thromboplastin time in healthy volunteers (600 mL/day cranberry juice[E]).[32] *See also note E*.	**Monitor** (low level of risk at typical doses).
Dong Quai *Angelica polymorpha*			
Antiplatelet and anticoagulant drugs	May potentiate effect of drug.	Herb Alone and with Drug Aspirin: Clinical study found inhibitory effect on arachidonic acid-induced platelet aggregation (2 of 24 healthy volunteers) and on epinephrine-induced platelet aggregation (1 of 24) after several days' consumption of dried root and rhizome (1 g/day). Bleeding was not reported in these participants. Taking with aspirin did not further suppress platelet function and prothrombin time was not impaired. Two other participants reported heavier menses, which were not associated with abnormality in platelet aggregation or thrombin generation.[49] Warfarin: Case reports (increased INR and PT;[50] increased INR and widespread bruising).[51]	**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 levels). All maintained an undetectable viral load.[52]	**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.)[53]	**Monitor** (low level of risk).
Dextromethorphan	May increase drug levels.	Clinical study (healthy volunteers): no effect in CYP2D6 extensive metabolizers; increase in AUC without increase in drug level in one poor metabolizer.[54]	**Monitor** (very low level of risk).
Immunosuppressant medication	May decrease effectiveness of drug.[1,55]	Theoretical concern based on immune-enhancing activity of Echinacea.	**Contraindicated**.
Midazolam	Decreases drug levels when drug administered intravenously.[G]	Clinical study (*E. purpurea* root).[54]	**Monitor** (medium level of risk) when drug administered intravenously.
Eleuthero (Siberian Ginseng) *Eleutherococcus senticosus*			
Atorvastatin	May cause liver injury due to high elevation of liver enzymes.	Case report (combination of "Siberian ginseng" and silymarin).[56]	**Monitor** (low level of risk).
Digoxin	May increase plasma drug levels.	Case report: apparent increase in plasma level, but herb probably interfered with digoxin assay[H] (patient had unchanged ECG despite apparent digoxin concentration of 5.2 nmol/L).[57] In a later clinical trial no effect observed on plasma concentration.[58]	**Monitor** (very low level of risk).
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.[59]	**Monitor** (very low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
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.[60-63] Anecdotal: garlic taken shortly before testing interferes with platelet aggregation in control subjects.[64] *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),[65-67] but no effect on platelet aggregation in one trial† (about 1.8 g/day, patients);[68] decreased serum thromboxane in one trial (3 g/day, healthy volunteers)[69]. † *See note J*. Clinical study (1.25–3.75 g/day): no effect on platelet aggregation, but women in the highest dose group experienced menorrhagia (as did women receiving 80 mg/day of aspirin) and nose bleeds were also reported in 24% of those receiving the highest dose of garlic.[70] *See note K*. 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.[71-73] Clinical studies (8–10 g/day of fresh garlic, healthy volunteers): inhibited platelet aggregation and increased clotting time.[74,75] Herb and Drug Aspirin: No published studies. Clopidogrel: Garlic tablet ("odorless", dose undefined) added to improve drug therapy, reduced platelet hyperactivity in two patients.[64] Warfarin: Two cases of increased INR and clotting times, very few details (garlic pearls, garlic tablets: dosage undefined).[76] Clinical trial: no effect in healthy volunteers (enteric-coated tablets equivalent to 4 g/day of fresh garlic).[47]	**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.	Ritonavir-boosted atazanavir: Case report (6 stir-fried garlic cloves three times per week).[77] Saquinavir: Two clinical studies (garlic extract, standardized for allicin content) with healthy volunteers[78,79] – in one study[79] the effect was minor with large variability in results.	**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).[1] Heartburn has been reported by some patients, although a review of clinical studies involving pregnant women using the herb found it to be a low risk.[80]	**Monitor** (low level of risk).
Antiplatelet and anticoagulant drugs	Phenprocoumon: May increase effectiveness of drug.	Case report (dosage undefined): increased INR.[81]	**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,[82] and coronary artery disease patients (10 g, single dose, dried ginger),[83] but no effect in healthy volunteers (2 g, single dose, dried ginger),[84] or coronary artery disease patients (4 g/day, dried ginger);[83] inhibition of platelet thromboxane production in healthy volunteers (5 g/day, fresh ginger).[85] Herb and Drug Two case reports (dose unknown): bleeding[86], increase in INR but no bleeding.[87] No pharmacokinetic or pharmacodynamic effects demonstrated in a clinical trial with healthy volunteers (3.6 g/day, dried ginger).[88] Epidemiological study: ginger (as a complementary medicine) was significantly associated with an increased risk of self-reported bleeding in patients taking warfarin.[89] These results should be viewed cautiously (*see note L*).	**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.
Crizotinib	May increase side effects of drug due to increased drug level.	Case report (grated ginger, honey, lemon juice and hot water, up to more than 1 L/day).[90]	**Monitor** (medium level of risk).
Nifedipine	May produce a synergistic antiplatelet effect.	Clinical study (1 g/day, dried ginger) in healthy volunteers and hypertensive patients.[91]	**Contraindicated**.

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Ginkgo[M] *Ginkgo biloba*			
Anticonvulsant medication eg carbamazepine, sodium valproate	May decrease the effectiveness of drug.	Case reports: two with well-controlled epilepsy,[92] others anecdotal and uncertain.[93-95] One of these[94] was subsequently analyzed as having probable causality (score 7)[B,96].	**Monitor** (medium level of risk). Increasing the intake of vitamin B6 may be advisable for patients taking anticonvulsants.[N]
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.[97] Herb Alone Rare case reports of bleeding.[98-100] Meta-analysis of randomized, placebo-controlled trials (healthy volunteers and patients): results indicate standardized Ginkgo extract does not increase the risk of bleeding.[101] Randomized, 5-year trial (elderly participants; Ginkgo 50:1 extract, 240 mg/day): no significant difference in incidence of hemorrhagic events.[102] 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.[97] *See also note P.* Aspirin: Case reports (2, bleeding;[98] one, extensive bruising after a fall – although possibly high Ginkgo dose (400 mg/day, undefined)).[103] Clinical studies: no additional effect on platelet function, platelet aggregation or bleeding time.[104-106] no increase in vascular adverse events, including hemorrhages, in acute stroke patients despite the high dose (Ginkgo preparation, providing 200 mg/day of flavone glycosides and 45 mg/day of terpene lactones; taken for 6 months).[107] 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;[108] no effect on pharmacokinetics or bleeding time, the increase in platelet aggregation was not significant (Ginkgo extract (undefined): 160 mg/day).[109] Clopidogrel: Case report (bruising and bleeding).[110] Clinical study with healthy volunteers (Ginkgo extract (undefined): single dose 120 mg) – no effect on platelet aggregation, bleeding times.[108] Ticlopidine: Case report (bleeding).[99] Clinical studies: no significant additional effect on bleeding time or platelet aggregation (Ginkgo 50:1 extract: single dose 80 mg; healthy volunteers),[111] and at the higher dose (120 mg/day) did not affect drug levels;[112] 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 significance is unknown (Ginkgo extract (undefined): 160 mg/day; pilot study of patients who had an acute ischemic stroke or transient ischemic attack),[113] improved antiplatelet effects in clopidogrel-resistant patients undergoing carotid stenting without hematologic or adverse effects, such as decreased platelet count, puncture-site hematoma (Ginkgo extract (undefined): 160 mg/day; small patient numbers).[114] Postmarketing study (80–160 mg/day of undefined Ginkgo extract): incidence of bleeding events in 4831 patients was 0.52% i.e. 25 patients; the severity was mild in 19 patients, moderate in 3 and severe in 3.[115] Warfarin: Case report (bleeding).[98] Clinical studies (healthy volunteers and patients): no additional effect on INR, platelet aggregation, coagulation parameters or plasma drug level.[88,116,117] A retrospective analysis of US veteran's medical records (2008-2014) found taking Ginkgo (dose and preparations unknown) concurrently with warfarin was significantly associated with higher risk of bleeding.[118] *See also note Q.*	**Monitor** (low level of risk), although additional caution may be warranted for the elderly and/or those taking warfarin.
Antipsychotic medication eg haloperidol, olanzapine, clozapine	General: May potentiate the efficiency of drug in patients with schizophrenia, by reducing symptoms.	Randomized, controlled trials (11; Ginkgo 50:1 extract: 120–360 mg/day), for schizophrenic patients taking haloperidol, olanzapine, clozapine, chlorpromazine, sulpiride, or a mixture (clozapine, chlorpromazine, sulpiride, perphenazine and haloperidol).[119,120] Five of 8 trials reported on adverse effects: no difference between Ginkgo and placebo for total scores, the results for subscores varied in two trials (generally favoring Ginkgo), but without serious side effects; in one trial, 2 patients who received placebo and experienced treatment failure were then treated with Ginkgo *alone* at double the dose (480 mg/day) and had severe delusions after about 2 weeks.[119]	Prescribe cautiously. **Reduce** drug if necessary in conjunction with prescribing physician.
	Risperidone: May potentiate adverse effects of drug or cause idiosyncratic reaction.	Two case reports (mood dysregulation, 160 mg/day of undefined extract;[121] priapism, 160 mg/day of undefined extract).[122] Incidence of adverse effects not significantly different between groups in two controlled studies (schizophrenia, dose unknown;[123] and autistic disorders in children 6 to 7 years, 80–120 mg/day of undefined extract).[124]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
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.)[125]	**Monitor** (low level of risk)
	HIV non-nucleoside transcriptase inhibitors eg efavirenz: May decrease drug levels and/ or cause virological breakthrough/failure.	Case report (decreased drug level and virological failure);[126] case report (increase in viral load after ongoing suppression; multiple supplements but the main one was an unspecified Ginkgo product (300 mg/day);[127] causality rated as probable (score 6)[8]).[96]	**Monitor** (medium level of risk).
Atorvastatin			
Benzodiazepines	May alter drug level.	Alprazolam: Clinical trial in healthy volunteers found no effect (Ginkgo 50:1 extract: 240 mg/day).[128] Diazepam: Clinical trial in healthy volunteers found no effect (Ginkgo 50:1 extract: 240 mg/day).[129] Midazolam: Clinical trials in healthy volunteers found conflicting results on drug levels: increased Ginkgo 50:1 extract: 360 mg/day),[130] decreased (Ginkgo 50:1 extract: 240 mg/day)[131] and no effect (Ginkgo 50:1 extract: 240 mg/day).[132]	**Monitor** (low level of risk).
Hypoglycemic drugs	General (sulfonylureas): May decrease the hypoglycemic activity. *See also Glipizide and Tolbutamide*	Theoretical extrapolation from clinical studies (very small numbers of participants): improved pancreatic beta-cell insulin production in response to glucose load (healthy/normal glucose tolerant individuals)[133] and in diabetics (only those with hyperinsulinemia treated with a range of oral hypoglycemic drugs and those with pancreatic exhaustion, and not diet-controlled diabetics i.e. those with medium to high insulin resistance), although no improvement in glucose metabolism (e.g. blood glucose) and no glycemia-related adverse effects – this suggests increased hepatic clearance of insulin and hypoglycemic agents.[134] Later study confirmed no adverse effect on insulin resistance (small number of healthy volunteers, prediabetics and diabetics taking oral hypoglycemic drugs).[135] Dose in each trial was Ginkgo 50:1 extract: 120 mg/day.	**Monitor** (low level of risk).
	Glipizide: May cause hypoglycemia.	Observation from aborted trial: hypoglycemia occurred in volunteers with normal glucose tolerance within 60 minutes.[136] Ginkgo 50:1 extract was administered as a single dose of 120 mg.[137]	**Monitor** (low level of risk).
	Metformin: May enhance effectiveness of drug.	Clinical trial with very small number of diabetics taking a variety of metformin daily doses (0.5–2.55 g; Ginkgo 50:1 extract: 120 mg/day): effect on pharmacokinetics of drug were not substantially altered in those taking 0.5 g/day or less of the drug. No effect observed in healthy volunteers.[136] Clinical trial (patients ineffectively managed): significantly improved glycemic parameters including HbA1c (Ginkgo 50:1 extract: 120 mg/day; metformin: 1.24 g/day).[138]	**Monitor** (low 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).[139]	**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);[130] pharmacokinetics not altered (Ginkgo 50:1 extract: 240 and 360 mg/day).[130,132]	**Monitor** (low level of risk).
Nifedipine	May increase drug levels or side effects.	Clinical studies found mixed results for mean plasma drug level: increase (120 mg/day, undefined),[140] although these results considered preliminary/inaccurate as AUC was not measured;[141] and no effect (240 mg/day; although results probably not robust as the herb was only administered for one day).[142] However, in the latter study, maximal plasma drug level and heart rate was increased with adverse drug reactions for participants with highest plasma drug levels (headache, dizziness, hot flashes).[142]	**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; AUC decreased by 27-42% depending on genotype)[143] and no effect (Ginkgo 50:1 extract: 240 mg/day).[132]	**Monitor** (low level of risk).
Statin drugs	May decrease drug levels.	Meta-analysis of 8 randomized controlled trials conducted in China (and of low methodological quality) found that compared with statins alone, the combination of statins and Ginkgo achieved significantly greater improvements in lipids in patients with dyslipidemia. *See also note R.* In four trials atorvastatin was administered, simvastatin in three and rosuvastatin in one trial.[144] Atorvastatin: Clinical study with healthy volunteers (Ginkgo 50:1 extract: 360 mg/day). No adverse pharmacodynamic effect was observed.[145] 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 there was a trend towards reduced ability to lower LDL-cholesterol.[146]	**Monitor** (low level of risk).
Tadalafil	May cause bleeding.	Case report (hematoma after surgery; patient also taking analgesics).[147]	**Monitor** (low level of risk).
Talinolol	May increase drug levels.	Clinical trial with healthy volunteers.[148]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Golden Seal *Hydrastis canadensis*			
Drugs which displace the protein binding of bilirubin eg phenylbutazone	May potentiate effect of drug on displacing bilirubin.	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).[149]	**Monitor** (low level of risk).
Midazolam	May increase drug level.	Clinical trial.[150]	**Monitor** (low level of risk).
Green Tea *Camellia sinensis* (See also Polyphenol-containing and/or 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).[151] However, a further *in vivo* animal study found EGCG was not antagonistic to the activity of the drug.[152] *See note S*.	**Contraindicated** at high doses (around 600 mg/day EGCG or 1 g/day green tea catechins).[†] More information required for doses below this level.
Digoxin	May decrease drug levels.	Clinical study with healthy volunteers (green tea extract providing 300 mg catechins).[153]	**Monitor** (medium level of risk at substantial doses of catechins).
Folate	May decrease absorption.	Clinical study with healthy volunteers.[154] 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 eg tacrolimus	May increase drug levels.	Case report (patient was a CYP3A4 poor metabolizer).[155]	**Monitor** (medium level of risk).
Nadolol	May increase drug levels.	Clinical studies with healthy volunteers (two single doses, simultaneous ingestion, green tea extract containing 52 mg and 156 mg catechins;[156] single dose, simultaneous and ingestion 1 hour prior, brewed green tea (4.5 g)),[157] although pulse rate and blood pressure were unchanged.[156]	**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.[158]	**Monitor** (low level of risk).
Statin drugs	May increase drug level and side effect of drug.	Fluvastatin: Clinical study with healthy volunteers. No significant effect on plasma concentrations for single doses of brewed green tea (300 mL) or extract providing 150 mg EGCG.[159] Rosuvstatin: Clinical study with healthy volunteers found a slight, likely clinically irrelevant, decrease in drug levels for ongoing administration (300 mg/day of EGCG).[160] Simvastatin: Case report of muscle pain, which is a known side effect (3 cups/day).[161] Subsequently analyzed as having probable causality (score 7)[8,96] Pharmacokinetic evaluation indicated green tea (1 cup, single dose) increased the bioavailability of simvastatin in this patient by a large amount (75%).[161] Ongoing administration of green tea beverage (healthy volunteers):[162] the increase was much smaller (7%; probably not clinically relevant), although in 25% of participants the increase was about 2-fold (dose: 335 mg/day of catechins); at a higher dose (638 mg/day of catechins), the increase in bioavailability was 28%, and the extent of the interindividual variability was similar.	**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.[163]	**Contraindicated**, unless **taken** at least 4 hours **apart**.
Warfarin	May decrease effectiveness of drug.	Case report (decreased INR; brewed green tea: 0.5–1 gallon/day).[164]	**Monitor** (very low level of risk).

* This chart is up-to-date as of January 2020.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Hawthorn *Crataegus monogyna, Crataegus laevigata (Crataegus oxyacantha)* (See also Polyphenol-containing and/or Tannin-containing herbs)			
Digoxin	May increase effectiveness of drug.	Clinical studies indicate a (beneficial) synergistic effect.[165,166] Pharmacokinetics not affected in a clinical study (healthy volunteers).[167]	**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),[168,169] decreased nonsignificantly (1 trial)[170] and was unchanged (1 trial).[171] Significant decrease in blood pressure observed in diabetics taking hypotensive drugs (1 trial).[172]	**Monitor** (low level of risk).
Horsetail *Equisetum arvense*			
Antiretroviral drugs	May cause virological breakthrough.	Two case reports (supplements containing horsetail).[173]	**Monitor** (medium level of risk).
Hypoglycemic herbs (See also Ginkgo, Korean Ginseng, Milk Thistle, St John's Wort)			
Hypoglycemic drugs including insulin	May potentiate hypoglycemic activity of drug.	Theoretical based on potential additive effects, although there are many examples of clinical trials in which herbs have been administered to diabetics who were using hypoglycemic medications, and despite improvements in glycemic parameters no adverse hypoglycemic effects were observed. Examples: ▪ 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.[174,175] ▪ 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 baseline fasting blood glucose above 8.0 mmol/L (144 mg/dL)).[176]	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*			
Antiplatelet and anticoagulant drugs	May potentiate effect of drug.	Herb Alone and with Drug Aspirin: Clinical study in Fiji with volunteers who were not kava drinkers (NKD), occasional (once/week; OKD) or regular drinkers (RKD: every week, 20 or more bowls/day). Platelet aggregation was in the normal range for all groups (baseline), but after single dose of aspirin (100 mg) there was a significant difference between NKD and RKD, and OKD and RKD, with the platelet aggregation *inhibited* (not decreased as much) in RKD. There was no significant difference between the groups when 300 mg was taken (aggregation decreased to a similar extent). The results suggest regular kava drinking (i.e. relatively high levels of kava lactones) may decrease aspirin sensitivity.[177]	**Monitor** (very low level of risk at typical doses).
CNS depressants eg alcohol, barbiturates, benzodiazepines	Potentiation of drug effects.	Theoretical concern based on deliberations of German Commission E[16] and the anxiolytic activity of kava.[1] Two apparent case reports (kava + benzodiazepines (alprazolam, flunitrazepam)).[178,179] Clinical trials with healthy volunteers: no additional side effects observed for kava (extract containing 240 mg/day of kava lactones) + benzodiazepine (bromazepam),[180] and kava (extract containing 210 mg/day of kavalactones) + alcohol.[181] Clinical study with healthy volunteers: no effect on pharmacokinetic parameters of midazolam (extract provided 253 mg/day of kavalactones).[150]	**Monitor** (low level of risk).
***L*-Dopa** and other Parkinson's disease treatments	Possible dopamine antagonist effects.	Case reports.[182,183] Although, kava is unlikely to be responsible for central dopaminergic antagonism (experimental model)[184] and kava reduced parkinsonism induced by neuroleptic drugs (observational study, psychiatric patients).[185]	**Contraindicated** unless under close supervision.
Other CNS drugs	May potentiate adverse effect possibly by decreased metabolism of drug.	Haloperidol: Case report (patient consumed kava beverage i.e. probable high dose).[186] Ropinirole: Case report (patient consumed kava beverage and kava tablets i.e. probable high dose).[186]	**Monitor** (low level of risk at typical doses).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
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.[1] 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.[187] 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,[188,189] those with metabolic syndrome,[190] type 2 diabetes[191] or glaucoma,[192] although baseline blood pressure may be a factor.[190] Herb and Drug Clinical trials: *decreased* blood pressure in essential hypertension,[193] and coronary artery disease[194] but no effect in white coat hypertension[193] and essential hypertension.[195]	**Monitor** (very low level of risk).
	Nifedipine: May increase drug levels.	Clinical trial (results considered preliminary/inaccurate as AUC was not measured, and species not defined).[140]	**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),[196,197] and decreased platelet aggregation.[196] (Dosage in Korea is generally high.) Clinical trial (healthy volunteers): inhibited platelet aggregation, but no effect on coagulation (PT, APTT).[198] Case reports: perioperative bleeding and impaired coagulation, possibly due to high preoperative intake of undefined ginseng (1 case);[199] postmenopausal women with spontaneous hematomas (3 cases).[200] Herb and Drug Aspirin: Clinical study found inhibitory effect on arachidonic acid-induced platelet aggregation (1 of 24 healthy volunteers) after several day's consumption of concentrated extract (providing 30 mg/day of ginsenosides); no clinically relevant bleeding events occurred. Taking with aspirin did not further suppress platelet function and prothrombin time was not impaired.[49]	**Monitor** (low level of risk).
	Acenocoumarol: May decrease effectiveness of drug.	Case report (decreased INR, herb dose unknown; causality rated as possible (score 4)[8]).[11]	**Monitor** (low level of risk).
	Warfarin: May decrease effectiveness of drug.	Herb and Drug Two cases reported (decreased INR without thrombotic episode, likely modest level of ginsenosides;[201] thrombosis, ginseng product undefined).[202] No effect demonstrated in three clinical trials (healthy volunteers and patients) for INR, prothrombin time and platelet aggregation.[203-205] Although the design of the trials has been criticized. *See note U*.[206]	**Monitor** (low level of risk).
CNS stimulants	May potentiate effects of drug.[1]	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: dosage unknown, causality rated as probable (score 6)[8]).[207]	**Monitor** (low level of risk).
Hypoglycemic drugs including insulin	May potentiate hypoglycemic activity of drug.[55]	Theoretical concern based on clinically observed hypoglycemic activity of ginseng in newly diagnosed type 2 diabetics.[208] 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.[209] Korean red ginseng (2.7 g/day) reduced the requirement for insulin in about 40% of diabetics in a small uncontrolled trial.[210] No adverse effects in three trials of type 2 diabetics well controlled with diet and/or oral hypoglycemic drugs.[199,211,212]	**Monitor** (low level of risk).
Imatinib	May potentiate adverse effect possibly by altered metabolism.	Case report (hepatotoxicity;[213] causality rated as probable (score 5)[8]).[96]	**Monitor** (low level of risk).
Lamotrigine	May cause side effect due to elevated drug level.	Case report (combined with deer antler velvet; DRESS syndrome; causality rated as probable (score 5)[8]).[214]	**Monitor** (medium level of risk).
MAO inhibitors eg phenelzine	May cause side effects such as headache, sleeplessness, tremor.	Case reports.[215-217]	**Contraindicated**.

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Midazolam	May decrease drug level.	Clinical studies with healthy volunteers: effect on drug levels conflicting – decreased (extract providing about 45 mg/day of ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg),[141] and no relevant effect (extracts providing about 62 mg/day of ginsenosides Rb1, Rb2, Rc, Re, Rg1;[218] and 85 mg/day of ginsenosides Rb1, Rb2, Rc, Rd, Re, Rg1, Rg3, Rh1).[219]	**Monitor** (low level of risk).
Sildenafil	May potentiate effects of drug.	Theoretical concern based on *in vitro* studies which show ginseng increases nitric oxide release from corpus cavernosum tissue.[220,221]	**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.[15,222]	**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.[15,222]	**Monitor** (low level of risk at typical doses).
Potassium-depleting agents eg thiazide diuretics, corticosteroids, licorice root (*Glycyrrhiza glabra*)	May increase potassium depletion.	German Commission E and ESCOP recommendation.[15,222]	**Avoid** excessive doses of laxatives. Maintain patients on a high potassium diet.
Licorice[v] *Glycyrrhiza glabra*			
Antihypertensive medications other than diuretics	General: May decrease effectiveness of drug.	When consumed in sufficient 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.[223] 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.[224] Dramatically elevated blood pressure with hypertensive retinopathy and nephropathy reported (225 mg/day of glycyrrhizin for 3 years).[225] 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[w]) taken for 2 weeks.[226-228] Other studies show variation of effects on blood pressure (*see note X*) – renal function may be a factor.[229] The increase in blood pressure after taking glycyrrhetinic acid (874 mg/day of glycyrrhizin) was more pronounced in salt-sensitive than salt-resistant volunteers.[230] The mechanism involves increased extracellular volume and enhanced pressure wave reflection from the peripheral circulation (licorice containing 290-370 mg/day of glycyrrhizin, taken for 2 weeks in normotensive volunteers),[231] although the results may be underestimated if measurements are taken only at rest.[232] 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.[233] Herb and Drug Case reports (licorice tea, 3 L/day; patient still hypertensive despite treatment with drugs;[234] decoction of Chinese herbs containing 5 g licorice, taken for 14 days).[235]	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[y] 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.[236] *See note Z.*	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[y] 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.[237]	**Monitor** (medium level of risk). Place patients on a high potassium diet.

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Drug	Potential Interaction	Basis of Concern	Recommended Action
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.[238] 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[227,229,239-245] and patients with essential hypertension[227] (ongoing oral administration): increase in urinary excretion of cortisol, but no significant change in plasma cortisol[227,229,239-245] (although plasma cortisone decreased)[239,240,246] and diurnal variation of plasma cortisol was unaffected.[242] Dosage was high: 100–200 g/day of licorice candy (containing glycyrrhizin or glycyrrhetinic acid equivalent to 262–2440 mg/day of glycyrrhizin[W]),[227,241,242,245] 3.5 g/day of licorice tablets (containing 266 mg/day of glycyrrhizin),[243] 4.8 g/day of licorice extract (containing glycyrrhetinic acid = 587 mg/day of glycyrrhizin),[244] 225 mg/day glycyrrhizin,[239] glycyrrhetinic acid (= 227–874 mg/day glycyrrhizin).[229,240] Clinical study with healthy volunteers and hypertensive patients (single dose, placebo-controlled; oral administration of glycyrrhetinic acid equivalent to 874 mg/day of glycyrrhizin[W]): increased plasma cortisol/cortisone ratio (due mostly to a decrease in plasma cortisone); salivary cortisol increased.[247] Clinical study with healthy volunteers (topical application of a cream containing glycyrrhetinic acid): no effect on plasma cortisol.[248] 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;[241] oral administration of glycyrrhetinic acid = 227 mg/day of glycyrrhizin[W] + oral cortisol to 2 volunteers).[249,250] *See also Note AA*. *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.[251]	**Monitor** (very low level of risk at typical 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;[W] prednisolone administered intravenously): increased drug level[252] and increased prednisolone/prednisone ratio[BB] in urine and plasma.[253] Dosage was high: 200 mg/day glycyrrhizin,[252] and 400 mg/day glycyrrhetinic acid (= 700 mg/day glycyrrhizin).[253]	**Monitor** (low level of risk at typical doses) when drug administered intravenously.
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.[223,254,255] 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.[256]	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[Y] 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.[257]	**Monitor** (low level of risk at typical doses).
	Thiazide and loop (potassium-depleting) diuretics: The combined effect of licorice and the drug could result in excessive potassium loss.[15]	Herb or Constituent Alone Hypokalemia demonstrated in case reports and clinical studies, usually from long-term intake and/or very high dose,[223,254,255] however effect has been demonstrated in patients for ongoing treatment with herbal medicines containing glycyrrhizin at doses of 80–240 mg/day.[258] Herb and Drug(s) Case reports, usually from long-term intake and/or very high dose,[234,254,259-265] however effect has been demonstrated for ongoing treatment of glycyrrhizin as low as 80 mg/day.[258] Clinical trial (candy containing 40 mg/day of glycyrrhizin): decreased plasma potassium, with 20% of healthy volunteers hypokalemic in the first week.[266] Retrospective cohort study: of 389 elderly patients treated with two licorice-containing Japanese traditional medicines for 6-2788 days, 24.2% developed hypokalemia and of these patients, 38.3% were coadministered potassium-lowering drugs (loop or thiazide diuretics, glucocorticoids or other glycyrrhizin-containing preparations (less frequently)).[267] Full dose of these products provides about 70 mg/day of glycyrrhizin.[268]	**Contraindicated** unless under close supervision at doses > 40 mg/day glycyrrhizin.

* This chart is up-to-date as of January 2020.

Drug	Potential Interaction	Basis of Concern	Recommended Action
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).[269]	**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).[270]	**Monitor** (low level of risk at typical doses).
Omeprazole	May decrease drug level.	Clinical study with healthy volunteers (potassium salt of glycyrrhizin, equivalent to 287 mg/day of glycyrrhizin).[271]	**Monitor** (low level of risk at typical doses).
Potassium-depleting drugs other than thiazide and loop diuretics eg corticosteroids, stimulant laxatives	May result in excessive potassium loss.	Concern based on known adverse effect of herb. 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.[223,254]	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[V] Place patients on a high potassium diet.
Terbutaline	May cause hypokalemia and apparent mineralocorticoid excess.	Case report ("nonspecific intake of licorice" with high intake of water (4–5 L/day) and excessive use of drug (3–4 times normal dose)).[272]	**Monitor** (very low level of risk under normal circumstances).
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 Polyphenol-containing and/or Tannin-containing herbs)			
Warfarin	May potentiate effects of drug.	Theoretical concern based on *in vivo* animal study demonstrating anticoagulant activity (dosage unavailable).[273]	**Monitor** (very low level of risk).
Milk Thistle[M] *Silybum marianum*			
Domperidone	Increases drug levels, and therefore potential toxic side effects.	Clinical study with healthy volunteers (silymarin: 1000 mg/day).[274]	**Contraindicated** at this dose, effect at typical doses not known.
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),[276] although insulin requirements unchanged in another trial (silymarin: 200 mg/day);[277] improved glycemic control in diabetics treated with hypoglycemic drugs (silymarin: 200 and 600 mg/day),[278,279] improved blood glucose, blood insulin and insulin resistance in PCOS patients treated with metformin (silymarin: 750 mg/day);[280] but no effect on glucose metabolism in NAFLD patients including those with insulin resistance (silymarin: 280 and 600 mg/day).[281,282]	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).[269]	**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).[283] *See note CC.*	**Monitor** (low level of risk).
Metronidazole	May decrease absorption of drug, by increasing clearance.	Clinical study with healthy volunteers (silymarin: 140 mg/day).[284]	**Monitor** (medium level of risk).
Nifedipine	May delay the absorption rate of drug.	Clinical study with healthy volunteers (2x silymarin: 280 mg, single dose), but bioavailability unchanged and pharmacodynamic effects were minor.[285]	**Monitor** (low level of risk).
Ornidazole	May increase drug levels.	Clinical study with healthy volunteers (silymarin: 140 mg/day).[286]	**Monitor** (medium level of risk).
Talinolol	May increase drug levels.	Clinical study with healthy volunteers (silymarin: 420 mg/day).[287]	**Monitor** (low level of risk).
Oregon Grape *Berberis aquifolium*			
Drugs that displace the protein binding of bilirubin eg phenylbutazone	May potentiate effect of drug on displacing bilirubin.	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).[149]	**Monitor** (low level of risk).

* This chart is up-to-date as of January 2020.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Phellodendron[D] *Phellodendron amurense*			
Drugs that displace the protein binding of bilirubin eg phenylbutazone	May potentiate effect of drug on displacing bilirubin.	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).[149]	**Monitor** (low level of risk).
Immunosuppressives	Cyclosporin: Increase drug levels.	Observations in some transplant patients.[288] Clinical studies (600 mg/day of berberine): increased drug level but no renal toxicity or chronic rejection occurred in renal transplant patients;[288] mixed results in healthy volunteers: no effect and increased drug level, possibly due to timing – when intake was separated by 12 hours, the pharmacokinetics were not substantially altered.[289] Regarded as a beneficial interaction in China, as berberine allows the dose of drug to be decreased.[288]	At substantial doses of berberine, **contraindicated** unless under close supervision and/or in contact with prescribing physician.
	Tacrolimus: Increase drug levels and hence, adverse effects.	Case report (600 mg/day of berberine in a 16-year-old);[290] causality rated as possible (score 4)[B]).[96]	**Monitor** (medium level of risk at substantial doses of berberine).
Midazolam	May increase drug levels.	Clinical trial with healthy volunteers (900 mg/day of berberine).[291]	**Monitor** (low level of risk).
Polyphenol-containing and/or Tannin-containing herbs[DD]			
Immunosuppressives eg cyclosporin	Decreases drug levels, due to impaired absorption or increased metabolism.	Three case reports, in transplant patients (2 L/day of a tea containing 9 herbs including peppermint, chamomile, lemon balm)); 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.[292] Interactions subsequently analyzed as having probable causality (score 7) for chamomile tea, and possible causalities (score 4) for the other teas[B].[96]	**Monitor** (medium level of risk). Also advisable not to take simultaneously.
Iron	Inhibition of non-heme iron[EE] absorption.	Clinical and epidemiological studies, many of which have investigated black tea, have produced mixed results, but overall, a substantial dose of polyphenols/tannins may inhibit iron absorption.[293-317] Results for green tea have been conflicting (adverse effect, no effect, beneficial effect) in the healthy and those with anemia and dosage may be a factor.[314, 318-327] Factors that affect the consistency of results include: timing of consumption;[FF] presence of inhibitors (such as phytate[GG]) and type of study (results from single test meals may exaggerate the effect of iron inhibitors and enhancers).[312] Inhibition more likely to occur in those with poor iron status and iron-deficiency anemia. Examples: ▪ Clinical study (using test meal): decreased absorption in healthy volunteers (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 catechin equivalents).[313] *See also note HH.* ▪ Mixed results in other studies (healthy volunteers; test meals): rosemary (32.7 mg of phenolic substances: rosmarinic acid, carnosol, carnosic acid)[314] and cayenne (high dose: 4.2 g, dried weight;[II] containing 25 mg polyphenols)[315] reduced absorption; chamomile[316] and turmeric (0.5 g, dried weight, containing 50 mg polyphenols)[315] did not. *See also note KK.* ▪ Crossover, multiple-dose study (test meals; 4-week periods of 30, 250 and 1500 mg/day of condensed tannins/procyanidins from grape seed extract): no effect on iron bioavailability and status in nonanemic women.[294] ▪ Clinical study: 1-hour time interval between consumption of a meal containing iron and drinking black tea reduced the inhibitory effects on iron absorption.[317] ▪ Case report with rechallenge: anemia caused by high intake of green tea (> 1.5 L/day, 5 days/week for 20 years).[321] Epidemiological studies: decreased serum ferritin and slight reduction in hemoglobin especially at high levels of green tea consumption but no increase in anemia (Japan);[322] higher serum hemoglobin and less anemia (China; presumably green tea).[328] Clinical study (150–300 mg/day EGCG): decreased absorption in healthy women with low iron stores when administered together with an iron solution. Results significant only at higher dosage.[326] Case report of iron-deficiency anemia (likely high dose of turmeric).[329] *See also note LL (potential effect of Milk Thistle).*	In anemia and where iron supplementation is required, **do not take simultaneously** with meals or iron supplements.

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Red Clover *Trifolium pratense*			
Antiplatelet and anticoagulant drugs	May potentiate effect of drug and/or cause bleeding.	Herb Alone Case report of bleeding from the nose and lips, bruising, hematuria with INR > 7 and "detection of warfarin in the patient's blood" despite no history of warfarin use (red clover and alfalfa tea: 5–6 cups/day for 2 weeks). Authors incorrectly assume red clover contains coumarins.[330] Case report of subdural hematoma with normal INR and impaired platelet function ("red clover extract containing 40 mg isoflavones" for 8–10 years).[331]	**Monitor** (very low level of risk).
Methotrexate	May improve insulin sensitivity.	Case report (severe vomiting and epigastric pain, liver function test normal; preparation strength and standardization unknown);[332] causality rated as possible (score 4)[B]).[96]	**Monitor** (low level of risk).
Rhodiola *Rhodiola rosea*			
SSRIs	Potentiation effects possible in regard to serotonin levels.	Escitalopram: Case report (superventricular tachycardia, possibly due to serotonin syndrome).[333] Paroxetine: Case report (some symptoms of serotonin syndrome).[334] Sertraline: Clinical trial (mild to moderate depression): significantly fewer adverse events in those taking herb and drug compared to drug alone.[335]	**Monitor** (very low level of risk).
Saw Palmetto *Serenoa repens*			
Antiplatelet and anticoagulant drugs	May potentiate effect of drug.	Herb Alone Case report (hemorrhage during surgery).[336] Clinical trials (BPH patients): *reduced* intraoperative bleeding from TURP procedure with preoperative use of liposterolic extract (2 trials); blood loss not different when compared with drug treatment (5-alpha reductase inhibitor; 1 trial).[337] Herb and Drug Case reports (2): increased INR (warfarin + simvastatin,[338] aspirin + clopidogrel;[339] – in the first case, the interaction may have been due to the vitamin E also present in the preparation;[338] 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 transplant recipients. Clinical study: markedly increased drug levels in healthy volunteers[340] given *S. sphenanthera* extract, providing 67.5 mg/day of deoxyschisandrin[MM]. Tacrolimus: Observations in some renal and liver transplant recipients. Clinical studies (*S. sphenanthera* extract): markedly increased drug levels in healthy volunteers[341] and transplant recipients,[342,343] given extract, providing 67.5 mg/day of deoxyschisandrin[MM]; in patients with idiopathic membranous nephropathy (extract, providing 33.75 mg/day of deoxyschisandrin);[344] reduced the dose of the drug required to treat patients with idiopathic membranous nephropathy (dose unknown),[345] and transplant recipients (extract, providing 22.5 mg/day of deoxyschisandrin).[346] Although the drug levels were increased, there were no adverse effects on allograph function, and graft survival appeared to be facilitated, in renal transplant recipients (dose not clearly defined, possibly extract, providing 22.5 mg/day of deoxyschisandrin).[347]	**Monitor** (medium level of risk at typical doses).
Midazolam	May increase drug levels.	Increased drug level, increase in sleeping time and increase in mild to moderate adverse effects found in healthy volunteers, given *S. sphenanthera* extract, providing 67.5 mg/day of deoxyschisandrin[MM].[348]	**Monitor** (low level of risk at typical doses).
Prescribed medication	May accelerate clearance from the body.	Theoretical concern based on *in vivo* animal studies demonstrating enhanced phase I/II hepatic metabolism.[349,350]	**Monitor** (low 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[MM].[148]	**Monitor** (low level of risk at normal doses).
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.

* This chart is up-to-date as of January 2020.

Drug	Potential Interaction	Basis of Concern	Recommended Action
St John's Wort[NN] *Hypericum perforatum* (See also Polyphenol-containing and/or Tannin-containing herbs)			
Ambrisentan	May decrease effectiveness of drug.	Clinical study with healthy volunteers:[351] effect on pharmacokinetics probably not clinically relevant (e.g. AUC decreased by 17-25% depending on genotype).	**Monitor** (low level of risk).
Amitriptyline	Decreases drug levels.[352]	Clinical study (patients with depression using hyperforin-rich extract).	**Monitor** (medium level of risk).
Anticonvulsants eg carbamazepine, mephenytoin, phenobarbitone, phenytoin	May decrease drug levels via CYP induction.[353-355]	Theoretical concern. An open clinical trial demonstrated no effect on carbamazepine pharmacokinetics in healthy volunteers.[356] Case report: increase in seizures in patient taking several antiepileptic drugs, two of which are not metabolized by cytochrome P450.[357] Clinical study (healthy volunteers; clinical significance unclear): increased excretion of a mephenytoin metabolite in extensive metabolizers, but not in poor metabolizers.[358] *See note PP.*	**Monitor** (low level of risk).
Antiplatelet, anticoagulant and antithrombotic drugs	Clopidogrel: May potentiate effects of drug.	Clinical studies: increased responsiveness (decreased platelet aggregation or improved residual platelet reactivity) in hyporesponsive volunteers and patients,[359-362] 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.[359,363]	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.[365]	**Contraindicated**.
	Rivaroxaban: May decrease plasma drug levels.	Clinical study with healthy volunteers.[364]	**Monitor** (medium level of risk).
	Warfarin: May alter INR (most frequently increase).	Case reports: decreased INR (nine cases), increased INR (three cases).[366-368] One of these cases[368] was subsequently analyzed as having probable causality (score 6)[B].[96] Clinical study with healthy volunteers (decreased drug level and INR).[203]	**Contraindicated**.
Bosentan	May alter drug levels.	Clinical study (healthy volunteers): minor decrease overall, but large interindividual variability occurred in clearance (from 51% decrease to up to 88% increase).[369]	**Monitor** (low level of risk).
Benzodiazepines	Decrease drug levels.	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)[370] and decrease.[371] Case report of successful use in alprazolam withdrawal (dried herb dose unknown).[372]	**Monitor** (medium level of risk).
		Midazolam: Clinical studies, with healthy volunteers.[373-375,391] Decrease in drug exposure correlated with increasing hyperforin dose.[373] Effect not regarded as clinically relevant for low (< 1 mg/day) hyperforin extracts.[373,375] Another study that administered a low-hyperforin product also found no clinically relevant interaction, however, the direction of the effect was opposite: there was an increase in drug level.[376]	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).[377]	**Monitor** (low level of risk).
beta-Blockers (topical)	May decrease effect of drug.	Case report.[378]	**Monitor** (low level of risk).
Calcium channel antagonists	Decreases drug levels.	Nifedipine: Clinical study.[379]	**Contraindicated**.
		Verapamil: Clinical study.[380]	**Contraindicated**.
Cancer chemotherapeutic drugs eg irinotecan, imatinib	Decreases drug levels.	Clinical studies.[381-384]	**Contraindicated**.
Clozapine	Decreases drug levels.	Case report.[385] (causality rated as probale (score 6)[B]).[96]	**Contraindicated**.
Dextromethorphan	May increase drug levels.	Clinical study (healthy volunteers).[376]	**Monitor** (low level of risk).
Digoxin	Decreases drug levels.	Clinical studies (several studies showed decrease, one study showed no effect)[370,386-388] but effect is dependent upon dose of herb and the hyperforin content.[388]	**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:[389] effect on pharmacokinetics probably not clinically relevant (eg plasma levels decreased by only 6%); drug-induced side effects were also reduced. Two of the 10 patients had an increase in AUC. *See also note QQ.*	**Contraindicated**.
Fexofenadine	May decrease drug levels.	Clinical studies (healthy volunteers).[390,391] Another study that administered a low-hyperforin product found no clinically relevant interaction, however, the direction of the effect was opposite: there was an increase in drug level.[376]	**Monitor** (low level of risk).

* This chart is up-to-date as of January 2020.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Finasteride	May decrease drug levels.	Clinical study with healthy volunteers.[392] Case report: PSA level elevated (due to decreased efficacy of drug?) in patient with BPH.[393]	**Contraindicated**.
HIV non-nucleoside transcriptase inhibitors eg nevirapine	Decreases drug levels.	Case report.[394]	**Contraindicated**.
HIV protease inhibitors eg indinavir	Decreases drug levels.	Clinical study (healthy volunteers).[395]	**Contraindicated**.
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.[396]	**Monitor** (low level of risk).
	Metformin: May affect glucose tolerance.	Herb Alone Mixed results in clinical studies with healthy volunteers – glucose tolerance reduced, due to reduced insulin secretion;[397] and improved glucose tolerance.[398] Herb and Drug Clinical study with healthy volunteers: no significant effect on pharmacokinetics, but glucose tolerance improved, due to enhanced insulin secretion.[399]	**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.[400]	**Monitor** (very low level of risk).
	Tolbutamide: May affect blood glucose.	Two clinical studies (healthy volunteers): no effect on pharmacokinetics,[370,374] but there was an increased incidence of hypoglycemia in the trial using hyperforin-rich extract (33 mg/day of hyperforin).[374]	**Monitor** (low level of risk).
Immunosuppressives	Decreases drug levels.	Cyclosporin: Case reports,[401-409] case series,[410,411] clinical studies (healthy volunteers,[391] patients[412,413]) Interaction is dependent upon the hyperforin content.[404,412] Tacrolimus: Case report and clinical studies.[414-416]	**Contraindicated** especially for high-hyperforin extracts.
Ivabradine	May decrease drug levels.	Clinical trial with healthy volunteers. No pharmacodynamic effect was observed.[417]	**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).[418]	**Monitor** (medium level of risk).
Methadone	Decreases drug levels, possibly inducing withdrawal symptoms.	Case reports.[419]	**Contraindicated**.
Methylphenidate	May decrease efficacy.	Case report,[420] but clinical significance unclear.	**Monitor** (low level of risk).
Morphine (oral)	May potentiate effects of drug.	Clinical study (healthy volunteers):[421] pain scores were decreased when morphine coadministered 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 (healthy volunteers; AUC decreased by 38-44% depending on genotype).[422] Another study that administered a low-hyperforin product found no effect.[376]	**Monitor** (low level of risk). Lower risk for low-hyperforin extracts.
Oral contraceptives	May increase metabolism and reduce effectiveness of drug.	Breakthrough bleeding reported which was attributed to increased metabolism of drug.[366,401] Clinical significance unclear. Cases of unwanted pregnancies have been reported.[423-425] Contradictory results for effect on bioavailability, hormone levels and ovulation demonstrated in three clinical studies, although some breakthrough bleeding occurred.[426-428] In one clinical trial an extract low in hyperforin did not affect plasma contraceptive drug levels or cause breakthrough bleeding.[429] Clinical trial: clearance of levonorgestrel at emergency contraceptive doses increased (not statistically significant).[430] Clinical study: antiandrogenic effect of contraceptive not affected.[431]	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.[432]	**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.[433-438]	**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.[439] Pravastatin: Clinical study, no effect on plasma level in healthy volunteers.[440] Rosuvastatin: Case report[441] (causality rated as possible (score 3)[8]).[96] Simvastatin: Two clinical studies, decrease in drug levels in healthy volunteers,[440] and small increases in serum total cholesterol and LDL-cholesterol in patients.[442]	**Monitor** blood cholesterol regularly (medium level of risk).

* This chart is up-to-date as of January 2020.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Talinolol	May decrease drug levels.	Clinical study (healthy volunteers).[443]	**Monitor** (medium level of risk).
Theophylline	May decrease drug levels.	Case report.[444] No effect observed in clinical study with healthy volunteers.[445]	**Monitor** (low level of risk).
Voriconazole	Decreases drug levels.	Clinical study.[446]	**Contraindicated**.
Zolpidem	May decrease drug levels (but with wide interindividual variability).[RR]	Clinical study (healthy volunteers).[447]	**Contraindicated**.
Tannin-containing herbs Refer to Polyphenol-containing and/or Tannin-containing herbs (above)			
Turmeric[SS] *Curcuma longa*			
Antiplatelet and anticoagulant drugs	May potentiate effect of drug.	Herb Alone and with Drug Aspirin: Clinical study found inhibitory effect on arachidonic acid-induced platelet aggregation in 5 of 24 healthy volunteers after several days' consumption of highly concentrated Turmeric extract (providing 475 mg/day of curcuminoids), no bleeding events were reported and no effect on platelet aggregation by other agonists. Taking with aspirin did not further suppress platelet function and prothrombin time was not impaired.[49]	**Monitor** (low level of risk).
Etoricoxib	May potentiate adverse hepatic effect of drug.	Case report of acute liver injury (long-term use of herb).[448]	**Monitor** (low level of risk).
Tacrolimus	May increase drug levels.	Case reports: nephrotoxicity in liver transplant patient; high dose with food, estimated at "15+ spoonfuls daily" starting roughly 10 days prior to rehospitalization[449] (causality rated as probable (score 7)[B]);[96] elevated drug level in transplant patient (meal containing a lot of turmeric).[450]	**Monitor** at high doses (medium level of risk).
Talinolol	May decrease drug levels.	Clinical study with healthy volunteers (300 mg/day of curcuminoids).No effect on pharmacodynamics (blood pressure or heart rate).[451]	**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.[452] However a clinical study found no potentiation with alcohol.[453] Case report of adverse effect with benzodiazepine drug (lorazepam)[454] – herb dosage undefined but likely high (tablet contained extracts of valerian and passion flower (*Passiflora incarnata*); causality rated as possible (score 3)[B]).[96] Alprazolam: Clinical study in healthy volunteers found no effect on drug levels (extract provided 11 mg/day total valerenic acids).[455]	**Monitor** (very low level of risk).
Willow Bark *Salix alba, Salix daphnoides, Salix purpurea, Salix fragilis* (See also Polyphenol-containing and/or Tannin-containing herbs)			
Warfarin	May potentiate effects of drug.	Clinical study observed very mild but statistically significant antiplatelet activity (extract containing 240 mg/day of salicin).[456]	**Monitor** (low level of risk).
Wormwood *Artemisia absinthium*			
Warfarin	May potentiate effects of drug.	Case report (gastrointestinal bleeding due to increased INR; ingestion of herb (although plant part undefined), the dose of which was increased after several days).[457] Subsequently analyzed as having possible causality (score 4)[B]).[96]	**Monitor** (medium level of risk).

CODE FOR RECOMMENDED ACTION

Contraindicated: Do not prescribe the indicated herb.

Monitor: Can prescribe the indicated herb at typical therapeutic doses 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); **BPH:** benign prostatic hyperplasia; **CNS:** central nervous system; **CYP:** cytochrome P450; **DRESS:** drug reaction with eosinophilia and systemic symptoms; **ECG:** electrocardiogram/graph; **EGCG:** epigallocatechin gallate; **GAS:** ginseng abuse syndrome; **HbA1c:** hemoglobin A1c, glycated hemoglobin; **HIV:** human immunodeficiency virus; **HRT:** hormone replacement therapy; **11beta-HSD2:** 11beta-hydroxysteroid dehydrogenase type 2; **IDA:** iron deficiency anemia; **INR:** international normalized ratio; **LDL:** low density lipoprotein; **NAFLD:** nonalcoholic fatty liver disease; **OCP:** oral contraceptive pill; **OPC:** oligomeric procyanidin; **PCOS:** polycystic ovary syndrome; **PSA:** prostate specific antigen; **PT:** prothrombin time; **SSRI:** selective serotonin reuptake inhibitors; **tds:** three times per day; **TURP:** transurethral resection of the prostate; **>:** 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.

* This chart is up-to-date as of January 2020.

MEDI HERB®

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 (these patients need to be monitored on a frequent, regular basis):
  - 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.
- Care should be exercised with patients who exhibit long-term use of laxative herbs or potassium-depleting 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.
- The use of antioxidants (including herbs) in conjunction with chemotherapy and radiotherapy for cancer is controversial. Health care professionals should be aware of the issues and make informed recommendation to their patients.

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

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. Pharmacokinetic parameters were unchanged. Pharmacodynamic interaction possible, but clinical relevance is not known: the small, statistically-significant effect was observed at this dose of andrographolide and the minimum therapeutic dose of midazolam.

B. Assessed using the Drug Interaction Probably Scale (DIPS). Total DIPS score of greater than 8 has highly probable causation, 5-8 is probable, 2-4 possible and a score of less than 2 denotes a doubtful causation. Note: this assessment does not consider the dose of the herb compared to normal therapeutic doses.

C. Chaste tree has been evaluated for treatment of premenstrual syndrome (5 trials)[458-462] and cyclical mastalgia (1 trial).[463] OCP use was permitted providing the dose was maintained throughout[458-460,462,463] or documented.[461] Three trials noted that 12.8%, 30.2% and 22.7% of those receiving the herb used concomitant OCPs. In these trials, the administered dose was equivalent to 72–270 mg/day of dried fruit.[458,461,462] Four of the trials were placebo-controlled,[458,459,462,463] one was uncontrolled[461] and one used magnesium as a comparator.[460] There were either no adverse events found or they were mild, and occurred with similar incidence rate to the placebo and comparator groups. For example, 4 events occurred in the 86 women who received chaste tree (180 mg/day of dried fruit; one case of intermenstrual bleeding), and 3 events occurred in the 84 who received placebo.[458] There was one case of mild interim spotting among 36 women treated with chaste tree (72 mg/day of dried fruit).[462] In the uncontrolled study, there were 5 cases of spotting among the 43 that completed the study (180 mg/day of dried fruit), and one woman withdrew from the study due to pregnancy which was described as not related to the herbal treatment.[461]

D. 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.[464]

E. 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 (e.g. 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.

F. The cranberry 'juice' administered was similar in concentration to a reference cranberry 'juice' containing about 25% cranberry juice,[465] but with a higher concentration of anthocyanins, and lower in catechins and organic acids. *See also note E.*

G. No effect overall when midazolam was administered orally: oral clearance and AUC were unchanged.

H. 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.[466]

J. 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,[467] and was said to provide 12 mg/day of alliin,[65,74] although there is some doubt as to the amount of allicin released from this brand of tablet from around 1995 to 2000.[468]

* This chart is up-to-date as of January 2020.

K. Although the contents of the garlic tablets were not defined in the published results, information obtained from the manufacturer of the product indicated the disclosed amount (1.25, 2.5, 3.75 g) corresponded to fresh weight of garlic.[469] All volunteers received aspirin and after a washout period, one of three doses of garlic.

L. 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.[470]

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

N. 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.[471] Poisoning by ginkgotoxin can be counteracted by vitamin B6,[471] in cases of poisoning it is administered by intravenous injection.[472,473] Ginkgotoxin is present in very small amounts in standardized Ginkgo leaf extracts,[474] but is below the detection limits in human plasma after oral doses (240 mg of 50:1 extract).[475] 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.[475] (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.

P. 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.[476] 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.[477]) Another randomized dementia prevention trial that enrolled 2854 patients found no significant difference in the incidence of hemorrhagic events between those receiving Ginkgo 50:1 extract (240 mg/day) or placebo. The treatment period was 5 years and compliance was 95%.[478] In Korea, Ginkgo extract is administered with ticlopidine for the prevention of ischemic stroke or acute coronary syndrome.[479]

Q. Final analysis included 722 142 records. The data was adjusted for age (75 years or older) and comorbidities. The hazard ratio was 1.38 (95% CI: 1.20-1.58, $p < 0.001$).

R. For example, the pooled results show a mean difference for serum levels of total cholesterol of -0.61 mmol/L (-23.6 mg/dL). The dose of *Ginkgo biloba* administered was reported as 120–576 mg/day, and it is likely (from information in the English abstracts of two of the trials) that this refers to standardized extract.

S. The *in vitro* reduction by EGCG was overcome when the concentration of the drug was increased (to a level expected clinically i.e. in plasma from the standard drug dose).[480] 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).[152]

T. 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).[151] 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.[481]

U. 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.

V. Information is provided for dried root and extracts containing glycyrrhizin. See elsewhere for information on extracts containing only a minimum amount of glycyrrhizin (deglycyrrhizinized licorice).

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

X. No effect on blood pressure in healthy volunteers in three studies (130 mg/day of glycyrrhetinic acid = 227 mg/day of glycyrrhizin, for 14 days;[229] licorice tablets (266 mg/day of glycyrrhizin) for 56 days;[243] 300 mg/day of potassium salt of glycyrrhizin = 287 mg/day of glycyrrhizin, for 14 days);[270] including where plasma renin levels were high (3.1 ng/mL/h),[243] 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.[482] Hypertension, or hyperkalemia, did not occur in acute ischemic stroke patients treated with licorice extract made from roasted root that provided 106 and 212 mg/day of glycyrrhizin, taken for up to 7 days.[483]

Y. 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.

Z. 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.

AA. Maximum plasma cortisol (exogenous) was not increased in one volunteer;[250] in the other, plasma (exogenous) cortisone/cortisol ratio decreased,[249] 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.

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

CC. 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.

DD. Polyphenols are considered to be a dietary factor responsible for influencing iron absorption. This is due to studies in the 1970s and 1980s that found inhibition of iron absorption by beverages such as tea and coffee, and by gallic acid, tannic acid, and to a lesser extent, chlorogenic acid. The potential effect of a food was estimated from its polyphenol content (measuring for example, galloyl groups, catechin equivalents, tannic acid equivalents etc), in addition to considering other factors including phytate and ascorbic acid.[484,485] The problem arises however, in the estimation of polyphenols, due to inaccuracies based on different methods of analysis,[485] and possibly, differences in classification. The term 'tannin' has 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. Historically, plant polyphenols have been broadly divided into proanthocyanidins (condensed tannins) and polymers of esters based on gallic and/or hexahydroxydiphenic acid and their derivatives (hydrolyzable tannins).[486] (This classification ignores flavonoids, which are also regarded as polyphenols.) The terms 'tannin' and 'polyphenol' have been used interchangeably. For example, the results of a clinical study are described:

* This chart is up-to-date as of January 2020.

"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".[311] Depending on the analytical method used, it is possible that the polyphenol content may actually be the content of tannins or tannins + polyphenols.[487] It is not known if herbs containing substantial amounts of flavonoids will have similar interactions, and this may depend on the chemical structure. In one of the studies listed, the researchers assessed a variety of "polyphenolic-containing" beverages: coffee (containing chlorogenic acid), herbs such as chamomile, lemon balm, vervain and peppermint containing monomeric flavonoids and black tea and cocoa which contained polymerized polyphenols. The polyphenol contents of the teas and cocoa were expressed as catechin equivalents and as chlorogenic acid for coffee.[313] It is difficult then, to assess how the iron-absorption research relates to herbs. Whilst some herbs have polyphenols, tannins, oligomeric procyanidins and phenolic acids (such as chlorogenic acid) as characteristic or prominent constituents, such as cayenne (*Capsicum annuum*), chamomile (*Matricaria recutita*), hawthorn (*Crataegus* spp.), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), it is probably only those herbs with a high content (e.g. 10% or higher) such as cinnamon (*Cinnamomum verum*), grape seed extract (*Vitis vinifera*), green tea (*Camellia sinensis*), meadowsweet (*Filipendula ulmaria*), raspberry leaf (*Rubus idaeus*), St John's wort (*Hypericum perforatum*), willow bark (*Salix* spp.) or those providing substantial amounts of a key constituent e.g. resveratrol from *Polygonum cuspidatum* that might inhibit iron absorption. Some herbs may contain constituents that improve iron absorption (e.g. ascorbic and organic acids in cranberry), and hence overall may be less of a concern.

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

FF. 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.[310]

GG. Sorghum also contains phytate. Both phytate and polyphenols inhibit nutrients such as iron.[488,489] Clinical studies (healthy volunteers): reduced iron absorption (sorghum containing 0.15% tannins)[490] and dose-dependent inhibiting effect for condensed tannins (dephytinized sorghum).[491]

HH. 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.[313] The type of polyphenols present, as well as the concentration, may affect iron absorption.

JJ. Administered in freeze-dried form (from 14.2 g, fresh weight), 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).[315]

KK. 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).[315]

LL. There may be implications for conditions of iron overload. Clinical study (black tea consumed with meals over one year): decrease of iron absorption (from a single test meal) and consequently reduced storage iron reaccumulation (but to a smaller, nonsignificant extent than expected from studies using single doses) in those with hemochromatosis.[492] Reduced serum ferritin levels in patients with beta-thalassemia major (clinical study; green tea consumed as a tea: 2.5 g in 150 mL of hot water, 3 times a day for 8 weeks),[493] and in a patient with beta-thalassemia intermedia (green tea consumed for 11 months).[494] Although concentrated extract of milk thistle (known as silymarin) is a complex of flavanolignans, which have different chemical structures to most of the polyphenols studied, a possible iron-chelating effect has been suggested in preliminary research involving 10 hemochromatosis patients (single dose: 140 mg; test meal);[495] and it has significantly reduced serum ferritin levels in patients with beta-thalassemia major in three of five controlled trials (small patient numbers; adults and children, 420 mg/day).[496]

MM. Fructus Schisandra has historically been defined as the fruit of *Schisandra chinensis* or *Schisandra sphenanthera* in traditional Chinese medicine. In more recent years, the Chinese Pharmacopoeia lists the two species under separate monographs, with separate and different minimum marker levels but with similar properties and indications.[497] 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.[498,499] Using these analyses as a guide, a maximum dose of *S. chinensis* extract equivalent to 4 g/day, would provide 10 mg/day of deoxyschisandrin.

NN. 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.[500] 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.[501]

PP. 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.[271,502]

QQ. Two of the 10 patients with the highest hyperforin levels prior to drug administration showed the greatest decrease in the AUC_0-∞ of docetaxel, for the other patients, no apparent correlation was observed.

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

SS. Information is provided for herb containing standard levels of active constituents. See elsewhere for information on more bioavailable forms.

* This chart is up-to-date as of January 2020.

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