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.
    - Except where specifically contraindicated, any patient on warfarin taking herbs should have their INR (international normalised ratio) closely monitored, especially when herbal treatment changes.
- 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 are potassium depleted,
    - 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-losing diuretics.
- Critical drugs should be taken at different times of the day from herbs (and food) to reduce chemical or pharmacokinetic interactions. They should be separated by at least 1 hour, preferably more.
- Stop all herbs approximately 1 week before surgery. St Mary's thistle may help reduce the toxic after-effects of anaesthetic 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.
- The use of antioxidants (including herbs) in conjunction with chemotherapy and radiotherapy for cancer is controversial. Practitioners should be aware of the issues and make informed recommendations to their patients.
- If more than one of the above cautions apply, and/or if patients are taking more than one drug, additional caution is required.

Further reading:

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

* This chart is up-to-date as at May 2021. For any questions please contact our Clinical and Technical Support on 1300 654 336.

Herb-Drug Interaction Chart

How to Read the Chart

The chart is read from left to right. The information in the Basis of Concern column provides a short summary of the evidence for the assumed rationale described in the Potential Interaction column. More details may be provided in the Basis of Concern column. A recommended action is suggested on a risk assessment of the evidence.

Unless indicated, it is assumed that the information in the Basis of Concern column refers to the concurrent intake of the herb and the drug. Additional headings indicate when this is not the case, for example, some authorities assume an interaction could occur between a herb and a drug if the herb has demonstrated a particular pharmacological activity, such as antiplatelet activity (hence use of the heading: Herb Alone).

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 **mediherb.com.au** and view the Herb-Drug Interaction Chart under the 'Resources' tab, look for the link to 'Prescribing Guidelines & Assessment of Risk'.

Examples

Italicised words represent the information in the Herb-Drug Interaction chart below.

St John's wort and Cancer chemotherapeutic drugs

Clinical studies found that *decreased drug levels* occurred in *patients and healthy volunteers* taking cancer chemotherapeutic drugs. It is recommended that St John's wort is *contraindicated* in patients taking cancer chemotherapeutic drugs.

St John's wort and Hypoglycaemic drugs (Gliclazide)

In a *clinical study with healthy volunteers* administration of St John's wort resulted in *increased clearance* of gliclazide, which *may reduce the drug's efficacy*, however, *glucose and insulin response to glucose loading were unchanged.*

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.

Willow Bark and Warfarin

A *clinical study* observed a *very mild but statistically significant antiplatelet activity* when a concentrated, standardised extract of the herb was administered *alone*.

For this type of potential interaction, it is postulated that the herb *may potentiate the effects of the drug*: an adverse effect may be observed because the antiplatelet activity may be stronger if a herb with antiplatelet activity is taken with an antiplatelet drug. Statistical significance demonstrated in the clinical trial for administration of the herb does not necessarily confer clinical relevance, and indeed it has been suggested that the *clinical relevance may be low*.

As it is possible that the result may not be clinically relevant, the potential interaction is considered *low risk* and a caution is recommended: the patient should be *monitored*.

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Potential Herb-Drug Interactions for Commonly Used Herbs*

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).
Baical Skullcap *Scutellaria baicalensis*			
Rosuvastatin	May decrease drug levels.	Clinical study with healthy volunteers using 150 mg/day of isolated constituent (baicalin; AUC decreased by 1.8-42% depending on genotype).[3]	**Monitor** (low level of risk).[B]
Barberry *Berberis vulgaris*			
Drugs that displace the protein binding of bilirubin e.g. 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).[4]	**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).[5] Case report of postoperative bleeding (bilberry extract undefined).[6] 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 haemorrhages without impairing coagulation.[7] Case report (rectal bleeding and haematuria with elevated INR; patient reported to consume "large amounts of bilberry fruits every day for five years").[8] Subsequently analysed as having doubtful causality using DIPS.[9]	**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)[C]).[10]	**Monitor** (low level of risk).
Black Cohosh *Actaea racemosa*			
Statin drugs e.g. atorvastatin	May potentiate increase in liver enzymes, specifically ALT.	Case report.[11]	**Monitor** (low level of risk).
Bladderwrack *Fucus vesiculosus*			
Hyperthyroid medication e.g. carbimazole	May decrease effectiveness of drug.	Theoretical concern due to natural iodine content.	**Contraindicated** unless under close supervision.
Thyroid replacement therapies e.g. thyroxine	May add to effect of drug.	Theoretical concern linked to a case report where "kelp" caused hyperthyroidism in a person not taking thyroxine.[12]	**Monitor** (low level of risk).
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)[C]).[10]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Bugleweed *Lycopus virginicus, Lycopus europaeus*			
Radioactive iodine	May interfere with administration of diagnostic procedures using radioactive isotopes.[13]	Case report.	Contraindicated.
Thyroid hormones	Should not be administered concurrently with preparations containing thyroid hormone.[14]	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.[15]	Monitor (low level of risk).
HIV protease inhibitors	May increase drug level.	Case report, in a patient with cirrhosis being evaluated for liver transplant.[16]	Monitor (low level of risk).
Immunosuppressant medication	May decrease effectiveness of drug.	Theoretical concern based on immune-enhancing activity of herb.[17]	Contraindicated.
Cayenne (Chilli Pepper) *Capsium* 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, chilli-spiced meal).[19]	Monitor (low level of risk).
Celery Seed *Apium graveolens*			
Thyroxine	May reduce serum levels of thyroxine.	Two case reports.[20]	Monitor (very low level of risk).
Chamomile *Matricaria chamomilla (See also Polyphenol-containing and/or Tannin-containing herbs)*			
Warfarin	May potentiate effects of drug.	Case report (internal bleeding; ingestion of tea made using 1 teaspoon of *'leaves'* (4–5 cups/day) + chamomile-based skin lotion (1 teaspoon to each leg, 4–5 times/day), species undefined; + camphor-based chest rub).[21] Subsequently analysed using DIPS as having doubtful,[9] and possible causality (score 3)[C]).[22]	Monitor (very low level of risk).
Chaste Tree *Vitex agnus-castus*			
Hormone-related medications e.g. 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.[23] There are several trials published in which the herb has been administered to women using OCP without causing unwanted pregnancy – *see note D*.	Monitor (low level of risk).
Coleus *Coleus forskohlii (Plectranthus barbatus)*			
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: standardised Coleus extract and forskolin).[24] More recent *in vivo* animal research: standardised Coleus extract reduced the anticoagulant activity of warfarin.[25]	Monitor (low level of risk).
Hypotensive medication	May potentiate effects of drug.	Theoretical concern based on ability of high doses of forskolin and standardised Coleus extract to lower blood pressure in normotensive and hypertensive animals.[26,27] Clinical data from weight management trials: no effect on blood pressure in three trials, trend toward lower blood pressure in one small study.[28,29] Clinical trial (dose-escalation in healthy volunteers; extract providing 25-100 mg/day of forskolin): no significant effect on blood pressure or heart rate.[30]	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*.[31]	Monitor (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Cranberry *Vaccinium macrocarpon*			
Immunosuppressives	May decrease drug levels.	Cyclosporin: Clinical study with healthy volunteers: no substantial effect (single dose, 240 mL cranberry juice).[32] Tacrolimus: Case report (2 g/day 'juice extracts'; causality rated as possible (score 4)[C]).[33]	**Monitor** (medium level of risk).
Midazolam	May increase drug levels.	Clinical trials with healthy volunteers: effect on drug levels conflicting – increased (double-strength juice[E], 240 mL tds)[34] and no effect (cranberry juice,[F] 200 mL tds).[35]	**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').[36,37]	**Monitor** (low level of risk).
Tacrolimus – *See Immunosuppressives above*			
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).[38-46] Clinical trials: no significant effect found in atrial fibrillation patients (250 mL/day cranberry juice cocktail),[47] or in patients on warfarin for a variety of indications (8 oz (236 mL)/day cranberry juice cocktail).[48] No effect on baseline INR, however, area under the INR-time curve increased by 30% in healthy volunteers (juice concentrate equivalent to 57 g of dry fruit/day).[49] No alteration of prothrombin time in patients on stable warfarin therapy (480 mL/day cranberry juice)[50] or of thromboplastin time in healthy volunteers (600 mL/day cranberry juice[F]).[35] *See also note E.*	**Monitor** (low level of risk at low doses).
Dan Shen *Salvia miltiorrhiza*			
Antiplatelet and anticoagulant drugs	Clopidogrel: May decrease effectiveness of drug.	Clinical trial with healthy volunteers (decreased drug levels and decreased pharmacodynamics: reduced the inhibition of platelet aggregation).[51] *See also note G.*	**Monitor** (medium level of risk).
	Warfarin: May potentiate effect of drug.	Case reports: increased INR.[52-54]	**Contraindicated**.
Midazolam	May decrease drug levels.	Clinical trial with healthy volunteers.[55]	**Monitor** (medium level of risk).
Devil's Claw *Harpagophytum* spp.			
Warfarin	May increase bleeding tendency.	Case report (purpura) with very few details, and described as "not confirmed".[56] Subsequently analysed as having doubtful causality using DIPS,[9] perhaps due to lack of information.	**Monitor** (very low level of risk).
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 adrenaline-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.[57] Herb and Drug Warfarin: Case reports (increased INR and PT;[58] increased INR and widespread bruising).[59]	**Monitor** (low level of risk).
Echinacea *Echinacea angustifolia, Echinacea purpurea*			
Antiretroviral drugs	HIV non-nucleoside transcriptase inhibitors e.g. 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.[60]	**Monitor** (low level of risk).
	HIV protease inhibitors e.g. 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.)[61]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Echinacea *Echinacea angustifolia, Echinacea purpurea* (continued)			
Dextromethorphan	May increase drug levels.	Clinical study (healthy volunteers): no effect in CYP2D6 extensive metabolisers; increase in AUC without increase in drug level in one poor metaboliser.[62]	**Monitor** (very low level of risk).
Immunosuppressant medication	May decrease effectiveness of drug.	Theoretical concern based on immune-enhancing activity of Echinacea.[1,63] Case report: exacerbation of cutaneous symptoms in patient with CADM (clinically amyopathic dermatomyositis; an autoimmune disorder) taking low-dose naltrexone (species, plant part and dosage unknown).[64]	**Contraindicated**.
Midazolam	Decreases drug levels when drug administered intravenously.[H]	Clinical study (*E. purpurea* root).[62]	**Monitor** (medium level of risk) when drug administered intravenously.
Evening Primrose Oil *Oenothera biennis*			
Antiplatelet and anticoagulant drugs	May potentiate effect of antiplatelet drugs e.g. by decreasing the formation of thromboxane and increasing formation of PGE_1.[65]	This may be an overly simplistic or a not completely correct interpretation of the mechanism of action of EPO. For example, although EPO may increase the formation of 1-series prostaglandins such as PGE_1, which inhibits platelet aggregation, it may also increase levels of other factors that facilitate platelet aggregation, such as thromboxane A_2.[66,67] Herb Alone Case report (transient but extensive purpura and petechiae in neonate; mother consumed raspberry tea and "a total of thirteen 500-mg capsules of evening primrose oil, vaginally and orally" a week before delivery).[68] Clinical studies: decreased platelet aggregation during 4 months of treatment (patients; 3 g/day, providing 240 mg/day of GLA),[69] and from week 4 to week 6 of an 8-week trial (patients; EPO providing 540 mg/day of GLA).[70] Decreased platelet aggregation in those with high aggregation but had no effect on those displaying normal platelet aggregation (healthy elderly; 2.4 g/day, providing 200 mg/day of GLA).[71] No significant effect on platelet aggregation in patients (3.2 g/day, providing 272 mg/day of GLA;[72] 4 g/day, providing 360 mg/day of GLA;[73] 1.2 and 4.8 g/day, providing 500 and 2000 mg/day of GLA)[74] and healthy volunteers (20 g/day, providing 1200 mg/day of GLA),[75] including the elderly (EPO providing 1000 mg/day of GLA).[76] Increase in bleeding time in patients (3 g/day, providing 240 mg/day of GLA)[69] and no effect in the healthy elderly (EPO providing 1000 mg/day of GLA).[76] In patients: decrease in serum level of the proaggregatory TxB_2 (3 g/day, providing 240 mg/day of GLA),[69] significant decrease in serum TxB_2 only at week 2 of an 8-week trial (patients; EPO providing 540 mg/day of GLA),[70] no change in plasma TxB_2 or PGE_1 (4 g/day, providing 360 mg/day of GLA),[77] decreased release of TxB_2 from platelets during spontaneous clotting (1.5 g/day, providing 135 mg/day of GLA),[78] no change in release of TxB_2 or PGE_1 from platelets (1.2 and 4.8 g/day, providing 500 and 2000 mg/day of GLA),[74] no change in release of thromboxane A_2 from platelets (3.2 g/day, providing 272 mg/day of GLA;[72] no change in amount of TxB_2 released into serum during clotting (4 g/day, providing 360 mg/day of GLA).[77] *Increase* in plasma TxB_2 in both treatment (20 mL/day, providing 1800 mg/day of GLA) and control (olive oil) groups of rheumatoid arthritis patients.[79] A counterbalancing effect was observed in healthy elderly treated with EPO, providing 1000 mg/day of GLA, for 2 months: TxB_2 formation in platelets decreased (potentially decreasing platelet aggregation) but vitamin E level in platelets also tended to decrease (potentially increasing platelet aggregation);[76] similarly, there were significant increases in DGLA (antithrombotic) and arachidonic acid (proaggregatory) and a decrease in EPA (antiaggregatory) in platelet phospholipids.[80]	**Monitor** (low level of risk).
Lithium	May reduce serum level of drug.	Case report: decreased drug level initially did not cause change in mood or functioning so no change made to drug dose, however, drug level continued to drop.[81]	**Monitor** (medium level of risk).
Phenothiazines	May decrease effectiveness of drug.	Reports of worsening epilepsy in schizophrenics. No causal association demonstrated and no effect observed in later trials.[82]	**Monitor** (very low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Garlic *Allium sativum (See also Hypoglycaemic 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 e.g. aspirin and warfarin. Herb Alone Case reports of increased bleeding with high garlic intake. In five of the six cases the bleeding occurred during or after surgery.[83-88] In an additional two cases, patients admitted to self medicating with garlic (dose unknown).[89] Anecdotal: garlic taken shortly before testing interferes with platelet aggregation in control subjects.[90] *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),[91-93] but no effect on platelet aggregation in one trial† (about 1.8 g/day, patients);[94] decreased serum thromboxane in one trial (3 g/day, healthy volunteers)[95]. † *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.[96] *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.[97-99] Clinical studies (8–10 g/day of fresh garlic, healthy volunteers): inhibited platelet aggregation and increased clotting time.[100,101] Herb and Drug Aspirin: No published studies. Clopidogrel: Garlic tablet ("odorless", dose undefined) added to improve drug therapy, reduced platelet hyperactivity in two patients.[90] Warfarin: Two cases of increased INR and clotting times, very few details (garlic pearls, garlic tablets: dosage undefined).[102] Clinical trial: no effect in healthy volunteers (enteric-coated tablets equivalent to 4 g/day of fresh garlic).[49]	**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).[103] Ritonavir-boosted darunavir: Two case reports (15 cloves/week; unspecified but substantial amounts in food), and viral rebound observed.[104] Saquinavir: Two clinical studies (garlic extract, standardised for allicin content) with healthy volunteers[105,106] – in one study[106] the effect was minor with large variability in results.	**Monitor** (medium level of risk).
Tacrolimus	May increase drug levels as a consequence of herb-induced liver injury.	Case report in a liver-transplant patient; causality rated as possible for HILI (score 4)[L] – dose was high,[107] with tablet of known release providing 9.6 mg/day, then rising to 19.2 mg/day of allicin.	**Monitor** (medium level of risk) for moderate and high doses in hepatically-impaired patients.

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Drug	Potential Interaction	Basis of Concern	Recommended Action
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 12 randomised controlled trials published up until July 2013 involving pregnant women using the herb found it to be a low risk.[108] A review of randomised clinical trials published up until July 2019, found 17 studies that provided information about adverse effects caused by ginger for the treatment of a variety of conditions. The incidence of heartburn in patients was individually reported in 11 trials, and excluding one trial,[M] ranged from 1.7% to 15.3%.[109] (This does not compare the incidence of heartburn with that of placebo or control. For example, in one trial the relative risk of heartburn in pregnant women for ginger (1 g/day, powder) compared to dimenhydrinate (100 mg/day) was 1.44, a difference which was not statistically significant.[108])	**Monitor** (low level of risk).
Antiplatelet and anticoagulant drugs	Phenprocoumon: May increase effectiveness of drug. Warfarin: Increased risk of spontaneous bleeding.	Concern based on potential to alter coagulation. Herb Alone Clinical studies: inhibition of platelet aggregation (5 g, divided single dose, dried ginger) in healthy volunteers,[110] and CAD patients (10 g, single dose, dried ginger),[111] but no effect in healthy volunteers (2 g, single dose, dried ginger),[112] or CAD patients (4 g/day, dried ginger; for 3 months);[111] inhibition of platelet thromboxane production in healthy volunteers (5 g/day, fresh ginger; for 7 days);[113] no effect on inhibition of platelet aggregation for 4 agonists, but did occur for adrenaline (tea made from 4 g/day, dried ginger; for 5 days) and no effect for any agonist at higher dose (tea made from 8 g/day).[114] Herb and Drug Phenprocoumon: Case report (dosage undefined): increased INR.[115] Warfarin: Two case reports (dose unknown): bleeding,[116] increase in INR but no bleeding.[117] Two case reports (China): increased INR (3 pieces/day of ginger, for 1 month; ginger vinegar (ginger steeped in vinegar for one week), unknown dose and duration).[118] No pharmacokinetic or pharmacodynamic effects demonstrated in a clinical trial with healthy volunteers (3.6 g/day, dried ginger).[119] Epidemiological study: ginger (as a complementary medicine) was significantly associated with an increased risk of self-reported bleeding in patients taking warfarin.[120] These results should be viewed cautiously (*see note N*).	Phenprocoumon Monitor at doses equivalent to < 4 g/day dried ginger (low level of risk). Warfarin 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).[121]	**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.[122]	**Contraindicated**.

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Ginkgo[P] *Ginkgo biloba*			
Anticonvulsant medication e.g. carbamazepine, sodium valproate	May decrease the effectiveness of drug.	Case reports: two with well-controlled epilepsy,[123] others anecdotal and uncertain.[124-126] One of these[125] was subsequently analysed as having probable causality (score 7)[C].[22]	**Monitor** (medium level of risk). Increasing the intake of vitamin B6 may be advisable for patients taking anticonvulsants.[Q]
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 haemorrhage was associated with elderly patients (65 years or older) who were taking Ginkgo alone.[127] Herb Alone Rare case reports of bleeding.[128-131] Meta-analysis of randomised, placebo-controlled trials (healthy volunteers and patients): results indicate standardised Ginkgo extract does not increase the risk of bleeding.[132] Randomised, 5-year trial (elderly participants; Ginkgo 50:1 extract, 240 mg/day, equivalent to 12 g/day of dried leaf): no significant difference in incidence of haemorrhagic events.[133] Herb and Drug Retrospective population-based study in Taiwan: the relative risk of haemorrhage associated with the use of Ginkgo extract combined with drugs (clopidogrel, cilostazol, ticlopidine, warfarin) was not significant.[127] *See also note R.* Aspirin: Case reports (2, bleeding;[128] one, extensive bruising after a fall – although possibly high Ginkgo dose (400 mg/day, undefined)).[134] Clinical studies: no additional effect on platelet function, platelet aggregation or bleeding time;[135,136,137] no increase in vascular adverse events, including haemorrhages, 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).[138] 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;[139] no effect on pharmacokinetics or bleeding time, the increase in platelet aggregation was not significant (Ginkgo extract (undefined): 160 mg/day).[140] Clopidogrel: Case report (bruising and bleeding).[141] Clinical study with healthy volunteers (Ginkgo extract (undefined): single dose 120 mg) – no effect on platelet aggregation, bleeding times.[139] Ticlopidine: Case report (bleeding).[129] Clinical studies: no significant additional effect on bleeding time or platelet aggregation (Ginkgo 50:1 extract: single dose 80 mg, equivalent to 4 g of dried leaf; healthy volunteers),[142] and at the higher dose (120 mg/day) did not affect drug levels;[143] increased inhibitory response of platelets to testing with two agonists (i.e. 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 ischaemic stroke or transient ischaemic attack),[144] improved antiplatelet effects in clopidogrel-resistant patients undergoing carotid stenting without haematologic or adverse effects, such as decreased platelet count, puncture-site haematoma (Ginkgo extract (undefined): 160 mg/day; small patient numbers).[145] 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.[146] Warfarin: Case report (bleeding).[128] Clinical studies (healthy volunteers and patients): no additional effect on INR, platelet aggregation, coagulation parameters or plasma drug level.[119,147,148] A retrospective analysis of US veteran's medical records (2008-2014) found taking Ginkgo (dose and preparations unknown) concurrently with warfarin was signific*antly associated* with higher risk of bleeding.[149] *See also note S.*	**Monitor** (low level of risk), although additional caution may be warranted for the elderly and/or those taking warfarin.
Antipsychotic medication	General: May potentiate the efficiency of drug in patients with schizophrenia, by reducing symptoms.	Randomised, controlled trials (11; Ginkgo 50:1 extract: 120–360 mg/day, equivalent to 6–18 g/day of dried leaf), for schizophrenic patients taking haloperidol, olanzapine, clozapine, chlorpromazine, sulpiride, or a mixture (clozapine, chlorpromazine, sulpiride, perphenazine and haloperidol).[150,151] 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 favouring 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.[150]	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;[152] priapism, 160 mg/day of undefined extract).[153] Incidence of adverse effects not significantly different between groups in two controlled studies (schizophrenia, dose unknown;[154] and autistic disorders in children 6 to 7 years, 80–120 mg/day of undefined extract).[155]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Ginkgo[P] *Ginkgo biloba* (continued)			
Antiretroviral drugs	HIV integrase inhibitors e.g. raltegravir: May alter drug levels	Clinical study with healthy volunteers (Ginkgo 50:1 extract: 240 mg/day, equivalent to 12 g/day of dried leaf) 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.)[156]	**Monitor** (low level of risk).
	HIV non-nucleoside transcriptase inhibitors e.g. efavirenz: May decrease drug levels and/or cause virological breakthrough/failure.	Case report (decreased drug level and virological failure);[157] case report (increase in viral load after ongoing suppression; multiple supplements but the main one was an unspecified Ginkgo product (300 mg/day);[158] causality rated as probable (score 6)[C]).[22]	**Monitor** (medium level of risk).
Benzodiazepines	May alter drug level.	Alprazolam: Clinical trial in healthy volunteers found no effect (Ginkgo 50:1 extract: 240 mg/day, equivalent to 12 g/day of dried leaf).[159] Diazepam: Clinical trial in healthy volunteers found no effect (Ginkgo 50:1 extract: 240 mg/day, equivalent to 12 g/day of dried leaf).[160] Midazolam: Clinical trials in healthy volunteers found conflicting results on drug levels: increased (Ginkgo 50:1 extract: 360 mg/day, equivalent to 18 g/day of dried leaf),[161] decreased (Ginkgo 50:1 extract: 240 mg/day, equivalent to 12 g/day of dried leaf)[162] and no effect (Ginkgo 50:1 extract: 240 mg/day, equivalent to 12 g/day of dried leaf).[163]	**Monitor** (low level of risk).
Hypoglycaemic drugs	General (sulfonylureas): May decrease the hypoglycaemic 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)[164] and in diabetics (only those with hyperinsulinaemia treated with a range of oral hypoglycaemic 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 glycaemia-related adverse effects – this suggests increased hepatic clearance of insulin and hypoglycaemic agents.[165] Later study confirmed no adverse effect on insulin resistance (small number of healthy volunteers, prediabetics and diabetics taking oral hypoglycaemic drugs).[166] Dose in each trial was Ginkgo 50:1 extract: 120 mg/day, equivalent to 6 g/day of dried leaf.	**Monitor** (low level of risk).
	Glipizide: May cause hypoglycaemia.	Observation from aborted trial: hypoglycaemia occurred in volunteers with normal glucose tolerance within 60 minutes.[167] Ginkgo 50:1 extract was administered as a single dose of 120 mg, equivalent to 6 g of dried leaf.[168]	**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, equivalent to 6 g/day of dried leaf): 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.[167] Clinical trial (patients ineffectively managed): significantly improved glycaemic parameters including HbA1c (Ginkgo 50:1 extract: 120 mg/day, equivalent to 6 g/day of dried leaf; metformin: 1.24 g/day).[169]	**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, equivalent to 6 g/day of dried leaf).[170]	**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, equivalent to 18 g/day of dried leaf);[161] pharmacokinetics not altered (Ginkgo 50:1 extract: 240 and 360 mg/day, equivalent to 12 and 18 g/day of dried leaf).[161,163]	**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),[171] although these results considered preliminary/inaccurate as AUC was not measured;[172] and no effect (240 mg/day, equivalent to 12 g/day of dried leaf; although results probably not robust as the herb was only administered for one day).[173] 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 flushes).[173]	**Monitor** at doses < 240 mg/day, equivalent to < 12 g/day of dried leaf (medium level of risk). **Contraindicated** for higher doses.

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Ginkgo[P] *Ginkgo biloba* (continued)			
Omeprazole	May decrease drug levels.	Clinical trials with healthy volunteers found conflicting results on drug levels: decreased (Ginkgo 50:1 extract: 280 mg/day, equivalent to 14 g/day of dried leaf; AUC decreased by 27-42% depending on genotype)[174] and no effect (Ginkgo 50:1 extract: 240 mg/day, equivalent to 12 g/day of dried leaf).[163]	**Monitor** (low level of risk).
Statin drugs	May decrease drug levels.	Meta-analysis of 8 randomised 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 dyslipidaemia. *See also note T.* In four trials atorvastatin was administered, simvastatin in three and rosuvastatin in one trial.[175] Atorvastatin: Clinical study with healthy volunteers (Ginkgo 50:1 extract: 360 mg/day, equivalent to 18 g/day of dried leaf). No adverse pharmacodynamic effect was observed.[176] Simvastatin: Clinical study with healthy volunteers (Ginkgo 50:1 extract: 240 mg/day, equivalent to 12 g/day of dried leaf) – 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.[177]	**Monitor** (low level of risk).
Tadalafil	May cause bleeding.	Case report (haematoma after surgery; patient also taking analgesics).[178]	**Monitor** (low level of risk).
Talinolol	May increase drug levels.	Clinical trial with healthy volunteers.[179]	**Monitor** (low level of risk).
Golden Seal *Hydrastis canadensis*			
Drugs which displace the protein binding of bilirubin e.g. 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).[4]	**Monitor** (low level of risk).
Midazolam	May increase drug level.	Clinical trials with healthy volunteers.[180,181]	**Monitor** (low level of risk).
Green Tea *Camellia sinensis (See also Polyphenol-containing and/or Tannin-containing herbs)*			
Antiplatelet and anticoagulant drugs	Aspirin: May potentiate bleeding. Warfarin: May decrease effectiveness of drug.	Herb Alone Clinical studies: decreased fibrinogen, PT and APTT, but no effect on bleeding time or clotting time in CAD patients (infusion; 4 g/day of leaf),[182] decreased plasma fibrinogen, but no effect on PT, APTT or INR (healthy volunteers; 2 cups/day),[183] higher PT and APTT in healthy volunteers who drank green tea (3 cups/day for at least 1 year) compared to those who did not.[184] Clinical studies with healthy volunteers: no effect on platelet aggregation or thromboxane production (7 cups/day, made from 6.3 g/day freeze-dried leaf 'powder', which provided 542 mg/day of total catechins),[185] no effect on haemostasis, including plasma fibrinogen (smokers; 2 groups: infusion made from freeze-dried leaf, 3 g/day of tea solids; concentrated extract, equivalent to 9 g/day of tea solids (18 cups/day),[186] no effect on blood coagulation, including fibrinogen or thromboxane formation (high fatty acid-rich diet; concentrated extract, equivalent to 10 g/day, providing 630 mg/day of the four main catechins),[187] no significant effect on maximum aggregation, but a decrease in the initial slope, which measures the initial rate of platelet aggregation (4 g/day leaf powder).[188] Herb and Drug Aspirin: Case report (vaginal bleeding, haematuria, bruising in postmenopausal diabetic; brewed green tea: 7–8 cups/day, for 6 months).[189] Warfarin: Case report (decreased INR; brewed green tea: 0.5–1 gallon/day).[190] Clinical study (healthy volunteers): statistically significant but insubstantial decrease in INR (1.44 to 1.39) and decreased PT (infusion, 6 g/day of leaf).[191] (*See also Vitamin K-containing herbs.*)	Aspirin **Monitor** (very low level of risk). Warfarin **Monitor** (low level of risk).
Boronic acid-based protease inhibitors e.g. bortezomib	May decrease efficacy of drug.	Theoretical concern based on initial *in vitro* data and *in vivo* animal study (green tea constituent: EGCG reduced tumour cell death induced by drug).[192] However, a further *in vivo* animal study found EGCG was not antagonistic to the activity of the drug.[193] *See note U.*	**Contraindicated** at high doses (around 600 mg/day EGCG or 1 g/day green tea catechins).[V] More information required for doses below this level.
Citalopram (Escitalopram)	May potentiate adverse effect (bleeding).	Case report of haemorrhage during surgery (1 cup/day; beverage and drug consumed for years; causality rated as possible (score 4)[C]).[194]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Green Tea *Camellia sinensis (See also Polyphenol-containing and/or Tannin-containing herbs)* (continued)			
Dapoxetine	May increase bioavailability of drug.	Clinical, single-dose study with healthy volunteers: increase of 30% at higher dose of 4 g of extract providing 1200 mg of catechins, but no effect at half this dose.[195]	**Monitor** (very low level of risk at low-moderate doses).
Digoxin	May decrease drug levels.	Clinical study with healthy volunteers (green tea extract providing 300 mg catechins).[196] Case report; few details provided; survey and review of medical file of hospitalised patient, although causality rated as possible (score 3)[C].[197]	**Monitor** (medium level of risk at substantial doses of catechins).
Folate	May decrease absorption.	Clinical study with healthy volunteers.[198] Clinical significance unclear, as was a one-day study (i.e. 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 e.g. tacrolimus	May increase drug levels.	Case report (patient was a CYP3A4 poor metaboliser).[199]	**Monitor** (medium level of risk).
Isoniazid	May potentiate adverse effect on liver.	Case report (green tea extract; solvent and dose unknown).[200] *See note W.*	**Contraindicated**.
Lisinopril	May decrease drug levels.	Clinical study with healthy volunteers (single dose, green tea extract providing 300 mg EGCG).[201]	**Monitor** (medium level of risk).
Midazolam	May increase drug levels.	Clinical, single-dose studies with healthy volunteers: no effect at doses of extract containing 60 mg and 600 mg of catechins, however substantial effect at dose of extract containing 1200 mg.[195,202]	**Monitor** (very low level of risk at low-moderate doses).
Nadolol	May decrease drug levels.	Clinical studies with healthy volunteers (two single doses, simultaneous ingestion, green tea extract containing 52 mg and 156 mg catechins;[203] single dose, simultaneous and ingestion 1 hour prior, brewed green tea (4.5 g), providing 539 mg of catechins),[204] although pulse rate and blood pressure were unchanged.[203]	**Monitor** (medium level of risk).
Raloxifene	May decrease drug levels.	Clinical study with small group of healthy volunteers: AUC decreased by 36%,[205] but dose undefined, other than 3 cups/day of brewed tea made from commerically-available tea bags.[206,207]	Assuming a moderate dose was prescribed: **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.[202]	**Monitor** (low level of risk).
Statin drugs	May affect drug level (if increase, may increase side effects).	Atorvastatin: Clinical study with healthy volunteers: decrease in drug levels for two single doses of green tea extract providing 150 mg and 300 mg of catechins; effect not dose dependent.[208] 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.[209] Rosuvstatin: Clinical study with healthy volunteers found a slight, likely clinically irrelevant, decrease in drug levels for ongoing administration (300 mg/day of EGCG).[210] Simvastatin: Case report of muscle pain, which is a known side effect (3 cups/day).[211] Subsequently analysed as having probable causality (score 7)[C].[22] Pharmacokinetic evaluation indicated green tea (1 cup, single dose) increased the bioavailability of simvastatin in this patient by a large amount (75%). Even without consuming green tea, drug dose was halved after 3 months due to leg discomfort.[211] Ongoing administration of green tea beverage (healthy volunteers):[212] 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.[213]	**Contraindicated**, unless **taken** at least 4 hours **apart.**
Warfarin – *See Antiplatelet and anticoagulant drugs above*			
Ziprasidone	May decrease effectiveness of drug.	Case report (green tea extract; probable high dose: 1.5 times the recommended dose of product).[214]	**Monitor** (low level of risk).

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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.[215,216] Pharmacokinetics not affected in a clinical study (healthy volunteers).[217]	**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),[218,219] decreased nonsignificantly (1 trial)[220] and was unchanged (1 trial).[221] Significant decrease in blood pressure observed in diabetics taking hypotensive drugs (1 trial).[222]	**Monitor** (low level of risk).
Horsetail *Equisetum arvense*			
Antiretroviral drugs	May cause virological breakthrough.	Two case reports (supplements containing horsetail).[223]	**Monitor** (medium level of risk).
Hypoglycaemic herbs *(See also Ginkgo, Korean Ginseng, St John's Wort, St Mary's Thistle)*			
Hypoglycaemic drugs, including insulin	May potentiate hypoglycaemic 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 hypoglycaemic medications, and despite improvements in glycaemic parameters no adverse hypoglycaemic 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 hypoglycaemic drug requirements in diabetics.[224,225] • 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 hypoglycaemic drugs was required (these patients had baseline fasting blood glucose above 8.0 mmol/L).[226]	Prescribe cautiously and monitor blood sugar regularly. **Warn** patient about possible hypoglycaemic 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.[227]	**Monitor** (very low level of risk at typical doses).
CNS depressants e.g. alcohol, barbiturates, benzodiazepines	Potentiation of drug effects.	Theoretical concern based on deliberations of German Commission E[14] and the anxiolytic activity of kava.[1] Two apparent case reports (kava + benzodiazepines (alprazolam, flunitrazepam)).[228,229] Clinical trials with healthy volunteers: no additional side effects observed for kava (extract containing 240 mg/day of kava lactones) + benzodiazepine (bromazepam),[230] and kava (extract containing 210 mg/day of kava lactones) + alcohol.[231] Clinical study with healthy volunteers: no effect on pharmacokinetic parameters of midazolam (extract provided 253 mg/day of kava lactones).[180]	**Monitor** (low level of risk).
L-Dopa and other Parkinson's disease treatments	Possible dopamine antagonist effects.	Case reports.[232,233] Although, kava is unlikely to be responsible for central dopaminergic antagonism (experimental model)[234] and kava reduced parkinsonism induced by neuroleptic drugs (observational study, psychiatric patients).[235]	**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).[236] Ropinirole: Case report (patient consumed kava beverage and kava tablets i.e. probable high dose).[236]	**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 (side effects caused from high doses of ginseng (species not defined), described in the early literature). 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.[237] 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 on blood pressure found in healthy volunteers,[238-242] those with metabolic syndrome,[243] type 2 diabetes[244,245] or glaucoma,[246] although baseline blood pressure may be a factor.[243] Significant *reduction* in diastolic blood pressure in men with metabolic syndrome,[247] and in systolic and diastolic pressures in prehypertensive individuals.[248] Case report (hypertensive crisis).[249] Herb and Drug Clinical trials: *decreased* blood pressure in essential hypertension,[250] prehypertension and stage I hypertension (34% of patients were taking antihypertensive medications)[251] and CAD[252] but no effect in white coat hypertension[250] and essential hypertension.[253]	**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).[171]	**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),[254,255] and decreased platelet aggregation.[254] (Dosage in Korea is generally high.) Clinical trial (healthy volunteers): inhibited platelet aggregation, but no effect on coagulation (PT, APTT).[256] Case reports: perioperative bleeding and impaired coagulation, possibly due to high preoperative intake of undefined ginseng (1 case);[257] postmenopausal women with spontaneous haematomas (3 cases).[258] 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.[57]	**Monitor** (low level of risk).
	Acenocoumarol: May decrease effectiveness of drug.	Case report (decreased INR, herb dose unknown; causality rated as possible (score 4)[C]).[10]	**Monitor** (low level of risk).
	Warfarin: May decrease effectiveness of drug.	Two cases reported (decreased INR without thrombotic episode, likely modest level of ginsenosides;[259] thrombosis, ginseng product undefined).[260] No effect demonstrated in three clinical trials (healthy volunteers and patients) for INR, prothrombin time and platelet aggregation.[261-263] Although the design of the trials has been criticised. *See note X.*[264]	**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 e.g. raltegravir	May potentiate adverse effect possibly by altered metabolism.	Case report (elevated liver enzymes: dosage unknown, causality rated as probable (score 6)[C]).[265]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Korean Ginseng *Panax ginseng* (continued)			
Hypoglycaemic drugs, including insulin	May potentiate hypoglycaemic activity of drug.[63]	Theoretical concern based on clinically observed hypoglycaemic activity of ginseng in newly diagnosed type 2 diabetics.[266] Clinical significance unclear. Herb Alone 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.[267] Korean red ginseng extract (providing 83 mg/day of total ginsenosides) improved serum glucose levels compared with placebo in unmedicated patients with impaired fasting glucose, impaired glucose tolerance and newly diagnosed type 2 diabetes, without adverse hypoglycaemic effects. Diet was monitored and did not change.[268] Herb with Drug and/or Diet Korean red ginseng powder (2.7 g/day) reduced the requirement for insulin in about 40% of diabetics in a small uncontrolled trial.[269] No adverse effects on glucose levels in four trials of type 2 diabetics well controlled with diet and/or oral hypoglycaemic drugs from a range of ginseng doses, including very high.[244,245,270,271] There were no statistically significant changes in fasting plasma glucose, HbA1c or insulin levels in a placebo-controlled trial of type 2 diabetics who took Korean red ginseng extract (providing 41 mg/day of total ginsenosides, of which ginsenosides Rb1, Rb2, Rc, Rd, Re and Rg1 made up 20 mg/day) for 24 weeks. Intake of their oral hypoglycaemic drugs was not changed during the trial. One patient of 70 who received ginseng dropped out due to deterioration of blood glucose, and this patient "did not properly take the prescribed antidiabetic drugs and had an uncontrolled diet".[272] Case report (hypoglycaemia in a diabetic well controlled with oral hypoglycaemic drugs and diet).[273] *See note Y.*	**Monitor** (low level of risk).
Imatinib	May potentiate adverse effect possibly by altered metabolism.	Case report (hepatotoxicity;[274] causality rated as probable (score 5)[C]).[22]	**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)[C]).[275]	**Monitor** (medium level of risk).
MAO inhibitors e.g. phenelzine	May cause side effects such as headache, sleeplessness, tremor.	Case reports.[276-278]	**Contraindicated**.
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),[172] and no relevant effect (extracts providing about 62 mg/day of ginsenosides Rb1, Rb2, Rc, Re, Rg1;[279] and 85 mg/day of ginsenosides Rb1, Rb2, Rc, Rd, Re, Rg1, Rg3, Rh1).[280]	**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.[281,282]	**Monitor** (very low level of risk).
Laxative (anthraquinone-containing) herbs e.g. aloe resin *(Aloe barbadensis, Aloe ferox),* senna *(Cassia* spp.*),* cascara *(Frangula purshiana),* 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.[14,283]	**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.[14,283]	**Monitor** (low level of risk at typical doses).
Potassium-depleting agents e.g. thiazide diuretics, corticosteroids, licorice root (*Glycyrrhiza glabra*)	May increase potassium depletion.	German Commission E and ESCOP recommendation.[14,283]	**Avoid** excessive doses of laxatives. Maintain patients on a high potassium diet.

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Licorice[Z] *Glycyrrhiza glabra*			
Albendazole	May elevate drug level (and potentially, adverse effects).	Case report (active metabolite drug levels constantly high, but no adverse effect observed; regularly consumed licorice-containing drink).[284]	**Monitor** (medium level of risk).
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.[285] Hypokalaemic 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.[286] Dramatically elevated blood pressure with hypertensive retinopathy and nephropathy reported (225 mg/day of glycyrrhizin for 3 years).[287] 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[AA]) taken for 2 weeks.[288-290] Other studies show variation of effects on blood pressure (*see note BB*) – renal function may be a factor.[291] The increase in blood pressure after taking glycyrrhetinic acid (874 mg/day of glycyrrhizin) was more pronounced in salt-sensitive than salt-resistant volunteers.[292] 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),[293] although the results may be underestimated if measurements are taken only at rest.[294] Clinical study to establish a no-effect level for glycyrrhizin (healthy female volunteers): significant results (e.g. 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.[295] Clinical study with asthma patients: significant increase in blood pressure for licorice extract providing 300 mg/day of glycyrrhizin for 4 weeks; little or no change for dose 200 mg/day of glycyrrhizin.[296] Pseudoaldosteronism did not occur in drug-medicated, depressed patients additionally treated with a salt of glycyrrhizin (432 mg/day of glycyrrhizin) for 4 weeks.[297] Case report (pseudoaldosteronism caused by a very small dose of licorice (ingredient of mouth freshener) taken for a long period (60 years)).[298] Herb and Drug Case reports (licorice tea, 3 L/day; patient still hypertensive despite treatment with drugs;[299] decoction of Chinese herbs containing 5 g licorice, taken for 14 days).[300]	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[CC] 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.[301] *See note DD.*	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[CC] Place patients on a high potassium diet.
Cilostazol	May cause hypokalaemia, which can potentiate the toxicity of the drug.	Case report (palpitations in a patient taking 150 mg/day of glycyrrhizin long-term (10 years), then drug added)). Serum potassium levels were stable prior to administration of drug i.e. adverse reaction occurred after addition of drug..[302]	**Monitor** (medium level of risk). Place patients on a high potassium diet.

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Licorice[Z] *Glycyrrhiza glabra* (continued)			
Corticosteroids	Cortisol (hydrocortisone), and associated drugs: 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.[303] 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 haemodialysis are not listed here.* Herb or Constituent Alone Clinical studies with healthy volunteers[289,291,304-310] and patients with essential hypertension[289] (ongoing oral administration): increase in urinary excretion of cortisol, but no significant change in plasma cortisol[289,291,304-310] (although plasma cortisone decreased)[304,305,311] and diurnal variation of plasma cortisol was unaffected.[307] Dosage was high: 100–200 g/day of licorice candy (containing glycyrrhizin or glycyrrhetinic acid equivalent to 262–2440 mg/day of glycyrrhizin[AA]),[289,306,307,310] 3.5 g/day of licorice tablets (containing 266 mg/day of glycyrrhizin),[308] 4.8 g/day of licorice extract (containing glycyrrhetinic acid = 587 mg/day of glycyrrhizin),[309] 225 mg/day glycyrrhizin,[304] glycyrrhetinic acid (= 227–874 mg/day glycyrrhizin).[291,305] Clinical study with healthy volunteers and hypertensive patients (single dose, placebo-controlled; oral administration of glycyrrhetinic acid equivalent to 874 mg/day of glycyrrhizin[AA]): increased plasma cortisol/cortisone ratio (due mostly to a decrease in plasma cortisone).[312] Clinical study with healthy volunteers (topical application of a cream containing glycyrrhetinic acid): no effect on plasma cortisol.[313] 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;[306] oral administration of glycyrrhetinic acid = 227 mg/day of glycyrrhizin[AA] + oral cortisol to 2 volunteers).[314,315] *See also note EE.* *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.[316]	Monitor (very low level of risk at typical doses).
	Cortisol (hydrocortisone), and associated drugs: May cause hypokalaemia.	Concern based on the known action of oral and intravenous administration of the drug (hydrocortisone can increase the loss of potassium). Case report: hypertension/mineralocorticoid excess caused by chronic licorice ingestion exacerbated by use of fludrocortisone (a drug which potently decreases potassium levels). Patient had persistently low blood potassium levels, but normal blood cortisol.[317]	When drug administered orally or by injection, avoid long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[CC] Place patients on a high potassium diet.
	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;[AA] prednisolone administered intravenously): increased drug level[318] and increased prednisolone/prednisone ratio[FF] in urine and plasma.[319] Dosage was high: 200 mg/day glycyrrhizin,[318] and 400 mg/day glycyrrhetinic acid (= 700 mg/day glycyrrhizin).[319] Herb and Drug Clinical study involving patients with acute exacerbation of COPD: combination increased FEV1 to a greater extent than herb or drug alone. Dosage of herb was high: 30 g, twice per day as decoction; methylprednisolone administered intravenously.[320]	Monitor (low level of risk at typical doses) when drug administered intravenously.
Digoxin	May cause hypokalaemia which can potentiate the toxicity of the drug.	Herb Alone Hypokalaemia 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.[285,321,322] 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.[323]	Avoid long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[CC] Place patients on a high potassium diet.

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Licorice[Z] *Glycyrrhiza glabra* (continued)			
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.[324]	**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.[14]	Herb or Constituent Alone Hypokalaemia demonstrated in case reports and clinical studies, usually from long-term intake and/or very high dose,[285,321,322] however effect has been demonstrated in patients for ongoing treatment with herbal medicines containing glycyrrhizin at doses of 80–240 mg/day.[325] Herb and Drug(s) Case reports, usually from long-term intake and/or very high dose,[299,321-332] however effect has been demonstrated for ongoing treatment of glycyrrhizin as low as 80 mg/day.[325] Clinical trial (candy containing 40 mg/day of glycyrrhizin): decreased plasma potassium, with 20% of healthy volunteers hypokalaemic in the first week.[333] Retrospective cohort study: of 389 elderly patients treated with two licorice-containing Japanese traditional medicines for 6-2788 days, 24.2% developed hypokalaemia and of these patients, 38.3% were coadministered potassium-lowering drugs (loop or thiazide diuretics, glucocorticoids or other glycyrrhizin-containing preparations (less frequently)).[334] Full dose of these products provides about 70 mg/day of glycyrrhizin.[335]	**Contraindicated** unless under close supervision at doses > 40 mg/day glycyrrhizin.
Immunosuppressives e.g. 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).[336]	**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).[337]	**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).[338]	**Monitor** (low level of risk at typical doses).
Potassium-depleting drugs other than thiazide and loop diuretics e.g. corticosteroids, stimulant laxatives	May result in excessive potassium loss.	Concern based on known adverse effect of herb. Herb Alone Hypokalaemia 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.[285,321]	**Avoid** long-term use at doses > 100 mg/day glycyrrhizin unless under close supervision.[CC] Place patients on a high potassium diet.
Terbutaline	May cause hypokalaemia 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)).[339]	**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).[340]	**Monitor** (very low level of risk).
Oregon Grape *Berberis aquifolium*			
Drugs that displace the protein binding of bilirubin e.g. 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).[4]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Peppermint *Mentha x piperita (See also Polyphenol-containing and/or Tannin-containing herbs)*			
Warfarin	May decrease effectiveness of drug.	Two case reports (decreased INR; menthol cough drops: 8–10 per day,[341] 6 per day[342]). Assuming the cough drops contained 5–10 mg of menthol, this is a dosage of about 30–100 mg/day of menthol.	**Monitor** (low level of risk at typical doses of herb).
	May potentiate effectiveness of drug.	Case report (increased INR, accompanied by gastrointestinal bleeding, 5 days after cardiac surgery – 3 cups of tea consumed on that day).[343]	**Monitor** (medium level of risk).
Phellodendron *Phellodendron amurense*			
Drugs that displace the protein binding of bilirubin e.g. 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).[4]	**Monitor** (low level of risk).
Immunosuppressives	Cyclosporin: Increase drug levels.	Observations in some transplant patients.[344] Clinical studies (600 mg/day of berberine): increased drug level but no renal toxicity or chronic rejection occurred in renal transplant patients;[344] mixed results in healthy volunteers, possibly due to timing: no effect (ongoing administration; intake separated by 12 hours) and increased drug level (single dose, to test concomitant intake).[345] Regarded as a beneficial interaction in China, as berberine allows the dose of cyclosporin to be decreased.[344]	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);[346] causality rated as possible (score 4)[C]).[22]	**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).[347]	**Monitor** (low level of risk).
Polyphenol-containing and/or Tannin-containing herbs[GG]			
Immunosuppressives e.g. 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.[348] Interactions subsequently analysed as having probable causality (score 7) for chamomile tea, and possible causalities (score 4) for the other teas[C].[22]	**Monitor** (medium level of risk). Also advisable not to take simultaneously.
Iron	Inhibition of non-haem iron[HH] 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.[349-373] Results for green tea have been conflicting (adverse effect, no effect, beneficial effect) in the healthy and those with anaemia and dosage may be a factor.[370,374-383] Factors that affect the consistency of results include: timing of consumption;[JJ] presence of inhibitors (such as phytate[KK]) and type of study (results from single test meals may exaggerate the effect of iron inhibitors and enhancers).[368] Inhibition more likely to occur in those with poor iron status and iron-deficiency anaemia. 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).[369] *See also note LL*. • Mixed results in other studies (healthy volunteers; test meals): rosemary (32.7 mg of phenolic substances: rosmarinic acid, carnosol, carnosic acid)[370] and cayenne (high dose: 4.2 g, dried weight;[MM] containing 25 mg polyphenols)[371] reduced absorption; chamomile[372] and turmeric (0.5 g, dried weight, containing 50 mg polyphenols)[371] did not. *See also note NN*. • 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 nonanaemic women.[350] • Clinical study: 1-hour time interval between consumption of a meal containing iron and drinking black tea reduced the inhibitory effects on iron absorption.[373] • Case report with rechallenge: anaemia caused by high intake of green tea (> 1.5 L/day, 5 days/week for 20 years).[377] Epidemiological studies: decreased serum ferritin and slight reduction in haemoglobin especially at high levels of green tea consumption but no increase in anaemia (Japan);[378] higher serum haemoglobin and less anaemia (China; presumably green tea).[384] 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.[382] Case report of iron-deficiency anaemia (likely high dose of turmeric).[385] Other Information • Olive leaf beverage (stabilised with ascorbic ac*id)* did not adversely affect haemoglobin or haemocrit values over 12 weeks in nonanaemic women.[386] • *See also note PP (iron overload generally and including potential effect of St Mary's Thistle).*	In anaemia 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, haematuria 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.[387] Case report of subdural haematoma with normal INR and impaired platelet function ("red clover extract containing 40 mg isoflavones" for 8–10 years).[388]	**Monitor** (very low level of risk).
Rhodiola *Rhodiola rosea*			
SSRIs	Potentiation effects possible in regard to serotonin levels.	Escitalopram (citalopram): Case report (superventricular tachycardia, possibly due to serotonin syndrome).[390] Paroxetine: Case report (some symptoms of serotonin syndrome).[391] Sertraline: Clinical trial (mild to moderate depression): significantly fewer adverse events in those taking herb and drug compared to drug alone.[392]	**Monitor** (low level of risk).
Sage *Salvia officinalis*			
Methadone	May potentiate adverse effect, possibly due to increased drug level.	Case report (respiratory distress and severe hypercapnia); few details provided; survey and review of medical file of hospitalised COPD patient, although causality rated as possible (score 3)[C].[197]	**Monitor** (low level of risk).
Saw Palmetto *Serenoa repens*			
Antiplatelet and anticoagulant drugs	May potentiate effect of drug.	Herb Alone Case report (haemorrhage during surgery).[393] Clinical trials: *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).[394] Herb and Drug Case reports (2): increased INR (warfarin + simvastatin,[395] aspirin + clopidogrel;[396] – in the first case, the interaction may have been due to the vitamin E also present in the preparation;[395] 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[397] given *S. sphenanthera* extract, providing 67.5 mg/day of deoxyschisandrin[QQ]. Tacrolimus: Observations in some renal and liver transplant recipients. Clinical studies (*S. sphenanthera* extract): markedly increased drug levels in healthy volunteers[398] and transplant recipients,[399,400] given extract, providing 67.5 mg/day of deoxyschisandrin[QQ]; in patients with idiopathic membranous nephropathy (extract, providing 33.75 mg/day of deoxyschisandrin);[401] reduced the dose of the drug required to treat patients with idiopathic membranous nephropathy (dose unknown)[402] and renal transplant recipients (extract, providing 22.5 mg/day of deoxyschisandrin).[403] 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).[404]	**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[QQ].[405]	**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 (high doses of herb extract or isolated constituents).[406,407]	**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[QQ].[179]	**Monitor** (low level of risk at typical doses).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Siberian Ginseng *Eleutherococcus senticosus*			
Atorvastatin	May cause liver injury due to high elevation of liver enzymes.	Case report (combination of Siberian ginseng and silymarin).[408] *See note RR.*	**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[SS] (patient had unchanged ECG despite apparent digoxin concentration of 5.2 nmol/L).[409] In a later clinical trial no effect observed on plasma concentration.[410]	**Monitor** (very low level of risk).
Slippery Elm Bark *Ulmus rubra*			
Prescribed medication	May slow or reduce absorption of drugs.	Theoretical concern based on absorbent properties of slippery elm.	**Take** at least 2 hours **away** from medication.
St John's Wort[TT] *Hypericum perforatum (See also Polyphenol-containing and/or Tannin-containing herbs)*			
Ambrisentan	May decrease effectiveness of drug.	Clinical study with healthy volunteers:[411] effect on pharmacokinetics probably not clinically relevant (e.g. AUC decreased by 17-25% depending on genotype).	**Monitor** (low level of risk).
Amitriptyline – *See Tricyclic antidepressants below*			
Anticonvulsants e.g. carbamazepine, mephenytoin, phenobarbitone, phenytoin	May decrease drug levels via CYP induction.[412-414]	Theoretical concern. An open clinical trial demonstrated no effect on carbamazepine pharmacokinetics in healthy volunteers.[415] Case report: increase in seizures in patient taking several antiepileptic drugs, two of which are not metabolised by cytochrome P450.[416] Clinical study (healthy volunteers; clinical significance unclear): increased excretion of a mephenytoin metabolite in extensive metabolisers, but not in poor metabolisers.[417] *See note UU.*	**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,[418-421] 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.[418,422]	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.[423]	**Contraindicated**.
	Rivaroxaban: May decrease plasma drug levels.	Clinical studies with healthy volunteers (pharmacokinetic and pharmacodynamic effects, in the order of 20-25% decrease).[424,425]	**Monitor** (medium level of risk).
	Warfarin: May alter INR (most frequently increase).	Case reports: decreased INR (nine cases), increased INR (three cases).[426-428] One of these cases[428] was subsequently analysed as having probable causality (score 6)[C.22] Clinical study with healthy volunteers (decreased drug level and INR).[261]	**Contraindicated**.
Antiretroviral drugs	May decrease drug levels.	HIV integrase inhibitors e.g. dolutegravir: Case report (monitoring of drug levels over several months found no effect for of intake of a tablet containing St. John's wort, passionflower and valerian).[429]	**Monitor** (very low level of risk).
		HIV non-nucleoside transcriptase inhibitors e.g. nevirapine: Case reports (decreased drug level).[430] HIV protease inhibitors e.g. indinavir: Clinical study (healthy volunteers).[431]	**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).[432]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
St John's Wort[TT] *Hypericum perforatum (See also Polyphenol-containing and/or Tannin-containing herbs)* (continued)			
Benzodiazepines	Decreases 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)[433] and decrease.[434] Case report of successful use in alprazolam withdrawal (dried herb dose unknown).[435]	**Monitor** (medium level of risk).
		Midazolam: Clinical studies, with healthy volunteers.[436-439] The increase in clearance was greater when drug administered orally than after intravenous injection.[439] Decrease in drug exposure correlated with increasing hyperforin dose.[436] Effect not regarded as clinically relevant for low (< 1 mg/day) hyperforin extracts.[436,438] 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.[440]	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).[441]	**Monitor** (low level of risk).
beta-Blockers (topical)	May decrease effect of drug.	Case report.[442]	**Monitor** (low level of risk).
Calcium channel antagonists	Decreases drug levels.	Nifedipine: Clinical study.[443] Verapamil: Clinical study.[444]	**Contraindicated.**
Cancer chemotherapeutic drugs e.g. irinotecan, imatinib	Decreases drug levels.	Clinical studies (patients and healthy volunteers).[445-447]	**Contraindicated.**
Clozapine	Decreases drug levels.	Case report[448] (causality rated as probable (score 6)[C]).[22]	**Contraindicated.**
Dextromethorphan	May increase drug levels.	Clinical study (healthy volunteers).[440]	**Monitor** (low level of risk).
Digoxin	Decreases drug levels.	Clinical studies (several studies showed decrease, one study showed no effect)[433,449-451] but effect is dependent upon dose of herb and the hyperforin content.[451]	**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:[452] effect on pharmacokinetics probably not clinically relevant (e.g. 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 VV.*	**Contraindicated.**
Fexofenadine	May decrease drug levels.	Clinical studies (healthy volunteers).[439,453] 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.[440]	**Monitor** (low level of risk).
Finasteride	May decrease drug levels.	Clinical study with healthy volunteers.[454] Case report: PSA level elevated (due to decreased efficacy of drug?) in patient with BPH.[455]	**Contraindicated.**
HIV non-nucleoside transcriptase inhibitors e.g. nevirapine – *See Antiretroviral drugs above*			
HIV protease inhibitors e.g. indinavir – *See Antiretroviral drugs above*			
Hypoglycaemic 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.[456]	**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;[457] and improved glucose tolerance.[458] Herb and Drug Clinical study with healthy volunteers: no significant effect on pharmacokinetics, but glucose tolerance improved, due to enhanced insulin secretion.[459]	**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.[460]	**Monitor** (very low level of risk).
	Tolbutamide: May affect blood glucose.	Two clinical studies (healthy volunteers): no effect on pharmacokinetics,[433,437] but there was an increased incidence of hypoglycaemia in the trial using hyperforin-rich extract (33 mg/day of hyperforin).[437]	**Monitor** (low level of risk).

* This chart is up-to-date as at May 2021. For any questions please contact our Clinical and Technical Support on 1300 654 336.

Drug	Potential Interaction	Basis of Concern	Recommended Action
St John's Wort[TT] *Hypericum perforatum (See also Polyphenol-containing and/or Tannin-containing herbs)* (continued)			
Immunosuppressives	Decreases drug levels.	Cyclosporin: Case reports,[461-469] case series,[470,471] clinical studies (healthy volunteers,[439] patients[472,473]). Interaction is dependent upon the hyperforin content.[464,472] Tacrolimus: Case report and clinical studies.[474-476]	**Contraindicated** especially for high-hyperforin extracts.
Ivabradine	May decrease drug levels.	Clinical trial with healthy volunteers. No pharmacodynamic effect was observed.[477]	**Monitor** (medium level of risk).
S-Ketamine (oral)	May decrease drug levels.	Clinical study with healthy volunteers. No pharmacodynamic effect was observed (e.g. analgesic effect not altered).[478]	**Monitor** (medium level of risk).
Methadone	Decreases drug levels, possibly inducing withdrawal symptoms.	Case reports.[479]	**Contraindicated**.
Methylphenidate	May decrease efficacy.	Case report,[480] but clinical significance unclear.	**Monitor** (low level of risk).
	May potentiate adverse effects of drug or cause idiosyncratic reaction.	Case reports (2: psychotic symptoms; mood and cognitive disturbance; causality rated as possible and probable, respectively by DIPS).[481]	**Monitor** (low level of risk).
Morphine (oral)	May potentiate effects of drug.	Clinical study (healthy volunteers):[482] pain scores were decreased when morphine coadministered with standardised 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).[483] Another study that administered a low-hyperforin product found no effect.[440]	**Monitor** (medium 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.[426,461] Clinical significance unclear. Cases of unwanted pregnancies have been reported.[484-486] Contradictory results for effect on bioavailability, hormone levels and ovulation demonstrated in three clinical studies, although some breakthrough bleeding occurred.[487-489] In one clinical trial an extract low in hyperforin did not affect plasma contraceptive drug levels or cause breakthrough bleeding.[490] Clinical trial: clearance of levonorgestrel at emergency contraceptive doses increased (not statistically significant).[491] Clinical study: antiandrogenic effect of contraceptive not affected.[492]	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.[493]	**Monitor** (medium level of risk).
SSRIs e.g. paroxetine, trazodone, sertraline **and other serotonergic agents** e.g. buspirone, nefazodone, venlafaxine	Potentiation effects in regard to serotonin levels.	Case reports:[494-501] clinical significance unclear, as most of these cases are poorly described, the causality has been questioned,[502-504] and the basis of concern requires a pharmacodynamic additive effect, but the mode of action of St John's wort is unlike conventional antidepressant drugs.[503]	**Monitor** (very low level of risk).[WW]
Statin drugs	May decrease effect and/or drug levels.	Atorvastatin: Clinical study, serum LDL-cholesterol increased by 0.32 mmol/L which corresponds to a decrease in effect of drug in patients by about 30%. Serum total cholesterol was also increased.[505] Pravastatin: Clinical study, no effect on plasma level in healthy volunteers.[506] Rosuvastatin: Case report[507] (causality rated as possible (score 3)[C]).[22] Simvastatin: Two clinical studies, decrease in drug levels in healthy volunteers,[506] and small increases in serum total cholesterol and LDL-cholesterol in patients.[508]	**Monitor** blood cholesterol regularly (medium level of risk).
Talinolol	May decrease drug levels.	Clinical study (healthy volunteers).[509]	**Monitor** (medium level of risk).
Theophylline	May decrease drug levels.	Case report.[510] No effect observed in clinical study with healthy volunteers.[511]	**Monitor** (low level of risk).
Tricyclic antidepressants	May decrease drug levels, and hence efficacy.	Amitriptyline: Clinical study (patients with depression using hyperforin-rich extract): decreased drug level.[512] Amitriptyline, imipramine or nortriptyline: Clinical study (patients): drug levels not measured but for the herb + drug group there was *greater* relief of depression, fewer gastrointestinal side effects, better sleep and less fatigue, compared to the placebo + drug group after 8 weeks.[513]	**Monitor** (medium level of risk).[WW]

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Drug	Potential Interaction	Basis of Concern	Recommended Action
St John's Wort[TT] *Hypericum perforatum (See also Polyphenol-containing and/or Tannin-containing herbs)* (continued)			
Voriconazole	Decreases drug levels.	Clinical study (healthy volunteers).[514]	Contraindicated.
Zolpidem	May decrease drug levels (but with wide interindividual variability).[XX]	Clinical study (healthy volunteers).[515]	Monitor (low level of risk).
St Mary's Thistle[P] *Silybum marianum*			
Domperidone	Increases drug levels, and therefore potential toxic side effects.	Clinical study with healthy volunteers (silymarin: 1000 mg/day).[516]	Contraindicated.
Hypoglycaemic drugs, including insulin	May improve insulin sensitivity.	No effect on tolbutamide in healthy volunteers (silymarin: 420 mg/day).[517] Controlled trials: improved glycaemic control and reduced insulin requirements in patients with type 2 diabetes and cirrhosis (silymarin: 600 mg/day),[518] although insulin requirements unchanged in another trial (silymarin: 200 mg/day);[519] improved glycaemic control in diabetics treated with hypoglycaemic drugs (silymarin: 200 and 600 mg/day),[520,521] improved blood glucose, blood insulin and insulin resistance in PCOS patients treated with metformin (silymarin: 750 mg/day);[522] but no effect on glucose metabolism in NAFLD patients including those with insulin resistance (silymarin: 280 and 600 mg/day).[523,524]	Prescribe cautiously and monitor blood sugar regularly. Warn patient about possible hypoglycaemic effects. Reduce drug if necessary in conjunction with prescribing physician.
Immunosuppressives e.g. 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).[336]	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).[525] *See note YY.*	Monitor (low level of risk).
Methadone	May reduce metabolism, increase exposure of drug leading to increased serotonin activity.	Case report (after regular use, increased daily dose to "a full fist of seeds").[526]	Monitor (medium level of risk) at high doses.
Metronidazole	May decrease absorption of drug, by increasing clearance.	Clinical study with healthy volunteers (silymarin: 140 mg/day).[527]	Monitor (medium level of risk).
Nifedipine	May delay the absorption rate of drug.	Clinical study with healthy volunteers (silymarin: 2 x 280 mg, single dose), but bioavailability unchanged and pharmacodynamic effects were minor.[528]	Monitor (low level of risk).
Ornidazole	May increase drug levels.	Clinical study with healthy volunteers (silymarin: 140 mg/day).[529]	Monitor (medium level of risk).
Talinolol	May increase drug levels.	Clinical study with healthy volunteers (silymarin: 420 mg/day).[530]	Monitor (low level of risk).
Tannin-containing herbs *Refer to Polyphenol-containing and/or Tannin-containing herbs (above)*			

* This chart is up-to-date as at January 2020. For any questions please contact our Clinical and Technical Support on 1300 654 336.

Drug	Potential Interaction	Basis of Concern	Recommended Action
Turmeric[zz] *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.[57] Herb with Drug Case report (increased INR in a patient taking a "turmeric containing product" and warfarin); few details provided.[531] Case report (gastrointestinal bleeding in a patient taking clopidogrel); few details provided; survey and review of medical file of hospitalised patient, although causality rated as probable (score 5)[C].[197]	**Monitor** (low level of risk).
Etoricoxib	May potentiate adverse hepatic effect of drug.	Case report of acute liver injury (long-term use of herb).[532]	**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 rehospitalisation[533] (causality rated as probable (score 7)[C];[22] elevated drug level in transplant patient (meal containing a lot of turmeric).[534]	**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).[535]	**Monitor** at high doses (≥ 300 mg/day curcumin, low level of risk).
Valerians Mexican Valerian *(Valeriana edulis),* Valerian *(Valeriana officinalis)*			
CNS depressants or alcohol	May potentiate effects of drug.	Theoretical concern expressed by US Pharmacopeial Convention.[536] However a clinical study found no potentiation with alcohol.[537] Case report of adverse effect with benzodiazepine drug (lorazepam)[538] – herb dosage undefined but likely high (tablet contained extracts of valerian and passionflower (*Passiflora incarnata*); causality rated as possible (score 3)[C].[22] Alprazolam: Clinical study in healthy volunteers found no effect on drug levels (extract provided 11 mg/day total valerenic acids).[539]	**Monitor** (very low level of risk).
Vitamin K-containing herbs e.g. green-leaf herbs			
Warfarin	May decrease effectiveness of drug.	Vitamin K is a cofactor in coagulation, and warfarin is known to interact with foods that are rich in vitamin K.[540] Patients taking warfarin are advised to eat a balanced diet maintaining a consistent amount of vitamin K, and avoid drastic changes in dietary habits, such as eating large amounts of green leafy vegetables.[541] Although it is possible that herbs containing a large amount of vitamin K may interact with warfarin,[542] because the whole plant tissue is usually not ingested (such as with dietary vegetables), and vitamin K is fat soluble, the solvent used to prepare the herbal extract/preparation is a factor. *See note AAA. See also Green Tea entry* (the potential interaction is unlikely to be due to vitamin K content alone).[543]	**Monitor** (very low to medium level of risk, depending on vitamin K content and extraction solvent).
White Horehound *Marrubium vulgare*			
Warfarin	May potentiate effects of drug.	Case report (increased INR; ingestion of several bags of candy containing the herb within the prior week; causality rated as probable by DIPS.[544]	**Monitor** (medium 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.	Herb Alone Clinical study observed very mild but statistically significant antiplatelet activity (extract containing 240 mg/day of salicin),[545] although the clinical relevance may be low.[546]	**Monitor** (low level of risk).

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Drug	Potential Interaction	Basis of Concern	Recommended Action
Withania *Withania somnifera*			
Thyroxine	May potentiate effects of drug.	Theoretical concern based on stimulating effect on thyroid hormones. Herb Alone Case report (increased serum T4 level).[547] Clinical study (root extract, providing 30 mg/day of withanolides): improved serum T4 level in subclinical hypothyroid patients;[548] three bipolar patients in a clinical trial experienced small increases in serum T4 from baseline (one had subclinical hypothyroidism),[549] after receiving extract made from leaf and root which probably provided 20–25 mg/day of withanolides for the first week, increasing to 40–50 mg/day of withanolides thereafter.[550,551] Placebo-controlled study with healthy volunteers: no significant effect on thyroid function (T3, T4, TSH);[552] – based on the brand name of the product, the dose of root extract provided 30 mg/day of withanolides.	**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).[553] Subsequently analysed as having possible causality using DIPS[9,22] (score 4)[C]).[22]	**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; **CAD**: coronary artery disease; **CNS**: central nervous system; **COPD**: chronic obstructive pulmonary disease; **CYP**: cytochrome P450; **DIPS**: Drug Interaction Probability Scale; **DGLA**: dihomo-gamma-linolenic acid; **DRESS**: drug reaction with eosinophilia and systemic symptoms; **ECG**: electrocardiogram/graph; **EGCG**: epigallocatechin gallate; **EPA**: eicosapentaenoic acid; **EPO**: evening primrose oil; **FEV1**: forced expiratory volume in one second; **GAS**: ginseng abuse syndrome; **GLA**: gamma-linolenic acid; **HbA1c**: haemoglobin A1c, glycated haemoglobin; **HILI**: herb-induced liver injury; **HIV**: human immunodeficiency virus; **HRT**: hormone replacement therapy; **11beta-HSD2**: 11beta-hydroxysteroid dehydrogenase type 2; **IDA**: iron deficiency anaemia; **INR**: international normalised ratio; **LDL**: low density lipoprotein; **NAFLD**: nonalcoholic fatty liver disease; **OCP**: oral contraceptive pill; **OPC**: oligomeric procyanidin; **PCOS**: polycystic ovary syndrome; **PG**: prostaglandin; **PSA**: prostate specific antigen; **PT**: prothrombin time; **SSRI**: selective serotonin reuptake inhibitor; **tds**: three times per day; **TSH**: thyroid stimulating hormone; **TURP**: transurethral resection of the prostate; **TxB2**: thromboxane B2; **T3**: triiodothyronine; **T4**: thyroxine; **>:** greater than; **≥:** greater than or equal to; **<**: less than.

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, beneficial 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. Analysis of Baical skullcap root samples from Japan found the baicalin content varied from 3.5 to 12%,[554] and for samples from China, the baicalin content can be higher (8.6–17.8%),[555] with the Chinese Pharmacopoeia specifying dried root should contain not less than 8% baicalin.[556] Extraction is best, at 43%, using 60% aqueous ethanol.[557] For a dose of 150 mg/day of baicalin, assuming the pharmacopoeial standard is met and 60% aqueous ethanol is used for extraction, 4.4 g/day of dried root would be required.

C. Assessed using the Drug Interaction Probability 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.

D. Chaste tree has been evaluated for treatment of premenstrual syndrome (5 trials)[558-562] and cyclical mastalgia (1 trial).[563] OCP use was permitted providing the dose was maintained throughout[558-560,562,563] or documented.[561] 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.[558,561,562] Four of the trials were placebo-controlled,[558,559,562,563] one was uncontrolled[561] and one used magnesium as a comparator.[560] 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.[558] There was one case of mild interim spotting among 36 women treated with chaste tree (72 mg/day of dried fruit).[562] 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.[561]

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,[564] but with a higher concentration of anthocyanins, and lower in catechins and organic acids. *See also note E.*

G. In China, dan shen is said to be combined with clopidogrel for the treatment of coronary heart disease, and more effective than clopidogrel alone,[565] however this activity may not be relevant to use at usual doses as in these trials the herb, isolated constituents or derivatives were administered by injection or dan shen was taken orally with other herbs (particularly *Panax notoginseng*).

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

J. These four trials used tablets containing a concentrated, standardised extract. A dosage of 900 mg/day of dry extract was equivalent to about 2.7 g/day of fresh garlic,[566] and was said to provide 12 mg/day of alliin,[91,100] although there is some doubt as to the amount of allicin released from this brand of tablet from around 1995 to 2000.[567]

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.[568] All volunteers received aspirin and after a washout period, one of three doses of garlic.

L. Assessed using the RUCAM (Roussel Uclaf Causality Assessment Method). The items for assessment are scored between -3 and +3, and the total score for the case can range from +14 to -9 points. Total score of 9 or greater has highly probable causation, 6-8 is probable, 3-5 possible, 1-2 unlikely and a score of 0 or less is excluded.

M. One trial investigated the effect of ginger on motion sickness and gastric function using single doses of ginger. Three of 8 volunteers reported heartburn, which appeared to be associated with the supine position required for the measurement of gastric emptying.[569]

N. 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.[570]

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

Q. 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.[571] Poisoning by ginkgotoxin can be counteracted by vitamin B6,[571] in cases of poisoning it is administered by intravenous injection.[572,573] Ginkgotoxin is present in very small amounts in standardised Ginkgo leaf extracts,[574] but is below the detection limits in human plasma after oral doses (240 mg of 50:1 extract, equivalent to 12 g of dried leaf).[575] 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.[575] (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.

R. 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.[576] 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.[577]) Another randomised dementia prevention trial that enrolled 2854 patients found no significant difference in the incidence of haemorrhagic events between those receiving Ginkgo 50:1 extract (240 mg/day, equivalent to 12 g/day of dried leaf) or placebo. The treatment period was 5 years and compliance was 95%.[578] In Korea, Ginkgo extract is administered with ticlopidine for the prevention of ischaemic stroke or acute coronary syndrome.[579]

S. 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, $p < 0.001$).

T. For example, the pooled results show a mean difference for serum levels of total cholesterol of -0.61 mmol/L. 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 standardised extract.

U. 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).[580] 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).[193]

V. 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).[192] 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.[581]

W. Rare cases of harm to the liver have been associated with products that contain green tea extracts, more frequently from concentrated extracts including those made using ethanol as the solvent and/or containing very high levels of catechins,[582,583] however, some cases have been reported after consumption of infusions, most probably due to an idiosyncratic reaction.[583] The number of human cases with hepatotoxicity associated with the consumption of green tea infusions is extremely low compared to the large number of consumers of green tea infusions.[583] However, given that isoniazid taken alone can cause hepatotoxicity even after many months of treatment,[584] combining isoniazid and green tea is not advised.

X. 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.

Y. Trade name of the product suggests the patient was taking *Panax ginseng* extract, equivalent to about 2.7 g/day, providing 24 mg/day of major ginsenosides.[585]

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

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

BB. 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;[291] licorice tablets (266 mg/day of glycyrrhizin) for 56 days;[308] 300 mg/day of potassium salt of glycyrrhizin = 287 mg/day of glycyrrhizin, for 14 days);[337] including where plasma renin levels were high (3.1 ng/mL/h),[308] 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.[586] Hypertension, or hyperkalaemia, did not occur in acute ischaemic 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.[587]

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

DD. ACE-inhibitors cause mild natriuresis (an increase in sodium excretion in the urine) and occasionally hyperkalaemia. 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 hypokalaemia caused by this dosage of glycyrrhizin.

EE. Maximum plasma cortisol (exogenous) was not increased in one volunteer;[315] in the other, plasma (exogenous) cortisone/cortisol ratio decreased,[314] 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.

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

GG. 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.[588,589] The problem arises however, in the estimation of polyphenols, due to inaccuracies based on different methods of analysis,[589] 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 (hydrolysable tannins).[590] (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: "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".[367] Depending on the analytical method used, it is possible that the polyphenol content may actually be the content of tannins or tannins + polyphenols.[591] 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 polymerised polyphenols. The polyphenol contents of the teas and cocoa were expressed as catechin equivalents and as chlorogenic acid for coffee.[369] 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.), lemon balm (*Melissa officinalis*), lime flowers (*Tilia cordata*), olive leaf (*Olea europaea*), peppermint (*Mentha* x *piperita*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), vervain (*Verbena officinalis*), it is probably only those herbs with a high content (e.g. 10% or higher) such as arjuna (*Terminalia arjuna*), bearberry (*Arctostaphylos uva-ursi*), cinnamon (*Cinnamomum verum*), grape seed extract (*Vitis vinifera*), green tea (*Camellia sinensis*), meadowsweet (*Filipendula ulmaria*), Pelargonium (*Pelargonium sidoides*), pomegranate peel (*Punica granatum*), propolis, raspberry leaf (*Rubus idaeus*), St John's wort (*Hypericum perforatum*), willow bark (*Salix* spp.), willow herb (*Epilobium parviflorum*) or those providing substantial amounts of a key constituent e.g. resveratrol from *Reynoutria japonica* 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.

HH. Haem iron is derived from haemoglobin and myoglobin mainly in meat products. Non-haem iron is derived mainly from cereals, vegetables and fruits.

JJ. 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.[366]

KK. Sorghum also contains phytate. Both phytate and polyphenols inhibit nutrients such as iron.[592,593] Clinical studies (healthy volunteers): reduced iron absorption (sorghum containing 0.15% tannins)[594] and dose-dependent inhibiting effect for condensed tannins (dephytinised sorghum).[595]

LL. 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.[369] The type of polyphenols present, as well as the concentration, may affect iron absorption.

MM. 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 chilli, as freeze drying probably decreased the ascorbic acid content (ascorbic acid enhances iron absorption).[371]

NN. 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).[371]

PP. 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 haemochromatosis.[596] Reduced serum ferritin levels in patients with beta-thalassaemia major who were treated with standard iron chelator (controlled clinical study; green tea consumed as a tea: 2.5 g in 150 mL of hot water, 3 times a day for 8 weeks),[597] and in a patient with beta-thalassaemia intermedia, not treated with standard iron chelator (green tea consumed for 11 months).[598] Addition of green tea consumption to usual treatment including standard iron chelator, significantly reduced liver iron concentration and serum ferritin in beta-thalassaemia intermedia patients (controlled clinical study; consumed as a tea: 2 g in a cup of water, 3 times a day, within one hour after meals for 12 months).[599] Although concentrated extract of St Mary's 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 haemochromatosis patients (single dose: 140 mg; test meal);[600] and it has significantly reduced serum ferritin levels in patients with beta-thalassaemia major in three of five controlled trials (small patient numbers; adults and children, 420 mg/day).[601]

QQ. 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.[556] 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.[602,603] 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.

RR. It is not known if either herb caused the adverse effect of the drug (for example, it may have been an idiosyncratic reaction, or caused by some other factor), whether both herbs together, or either herb, produced the effect. However, silymarin (210 mg/day) combined with simvastatin was used in a Chinese clinical trial involving patients with nonalcoholic steatohepatitis. Although there are few details available in English, no severe side effects occurred throughout the 12-week period, and ALT levels were decreased from baseline.[604,605]

SS. Eleutherosides from Siberian ginseng 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.[606]

TT. 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.[607] 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.[608]

UU. 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 metabolisers and poor metabolisers, the latter having a deficiency of CYP2C19 activity.[338,609]

VV. Two of the 10 patients with the highest hyperforin levels prior to drug administration showed the greatest decrease in the AUC¥ of docetaxel, for the other patients, no apparent correlation was observed.

WW. Antidepressant drugs are often combined in modern medicine. If clinically appropriate, St John's wort may be combined with antidepressant drugs under professional supervision, with the fully informed consent of the patient (many patients, and their doctors, may be concerned about the potential drug interactions). A low dose should be recommended at first both as a caution and to reassure the patient.[503] This is a general recommendation, based on the low likelihood of the herb having an adverse pharmacodynamic interaction with the drug, consideration however, needs to be given when prescribing, to evidence pointing to a pharmacokinetic interaction e.g. St John's wort and the tricyclic amitriptyline.

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

YY. 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 metabolised by CYP2C9. CYP2C9 is the main enzyme responsible for transforming losartan to its active metabolite.

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

AAA. For example, an analysis found that although the dried leaf of *Camellia sinensis* (green tea) may be rich in vitamin K1 (phylloquinone), brewed tea contains only a negligible amount. Two samples contained 1654 mcg, and 482 mcg, in 100 g of dried leaves. Brewed green tea, using the 482 mcg/100 g leaf sample, prepared according to standard methods and allowed to brew for 5 minutes, contained 0.03 mcg/100 mL (/100 g). Vitamin K1 remained to a large extent in the boiled leaf tissue (433 mcg/100 g).[610] (In comparison, broccoli and spinach contain about 200 mcg/100 g and 400 mcg/100 g, of phylloquinone respectively,[611] and generally larger quantities of vegetables are consumed, than herbs.) Therefore, an ethanolic extract of green tea could be expected to contain a higher vitamin K content than water extract. The content of vitamin K (phylloquinone usually, and occasionally dihydrophylloquinone) of herbs is usually higher than spices, and for a given herb, concentrations are generally higher in the dried than in the fresh form.[612] The following, relatively high, vitamin K contents (mcg/100 g) have been recorded: sage, dried: 1710; thyme, dried: 1710; chilli, dried: 106; dandelion leaves, fresh: 778; kale, fresh: 390. The following have contents in the range of about 15–30 mcg/100 g: dried cinnamon, spirulina and turmeric; fresh blueberries and globe artichoke. An undefined species of edible kelp, in fresh form, contains 66 mcg/100 g. In the following, vitamin K was found in very low levels (≤ 5 mcg/100 g): dried, oats; fresh and dried garlic and ginger; fresh cranberries.[613] There can however be variations in the vitamin K content, which may be influenced by cultivar, growing location and/or conditions, processing and storage. An analysis of herbs purchased from supermarkets in North America found dried sage to contain an average of 1040 mcg/100 g of phylloquinone (range: 844-1320), and for thyme the average was 1370 mcg/100 g (range: 1180-1550). It is suggested that herbs may be an overlooked source of vitamin K in the diet. It had been thought that vitamin K1 at levels of around 100 mcg/day from ongoing use of supplements were required to adversely affect warfarin anticoagulation, however even small amounts (25 mcg/day) given to patients with stable anticoagulation resulted in subtherapeutic INRs in vitamin-K depleted patients. In these patients even small changes in vitamin K intake was able to alter their coagulation status. Is the vitamin K content of medicinal herbs likely to cause an interaction with vitamin K antagonists such as warfarin? The main unknown is the efficiency of extraction from the plant tissue. Taking a content of 1710 mcg/100 g for dried thyme, assuming an aqueous ethanolic solution has an extraction efficiency of 100%, and at a dose of 1.5 g/day of dried herb, the dose of vitamin K1 could be as high as 25 mcg/day. With the vitamin K content in the dried herb not likely to always be this high, and the extraction efficiency unlikely to be 100%, it is possible, but not probable that a moderate dose of products containing thyme, and also sage, may provide vitamin K at a level of concern for some patients.

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