

Herb-Drug Interaction Chart

General Prescribing Guidelines

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- 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-depleting diuretics.
- Critical drugs should be taken at different times of the day from herbs (and food) to reduce chemical or pharmacokinetic interactions. They should be separated by at least 1 hour, preferably more.
- Stop all herbs approximately 1 week before surgery. 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.
- Interactions may be dose related for the herb and the drug, for example, St John's wort and digoxin.

- The use of antioxidants (including herbs) in conjunction with chemotherapy and radiotherapy for cancer is controversial. Practitioners should be aware of the issues and make informed recommendation 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.

Assessment of Risk & Recommended Action

An interaction may alter exposure to the drug and/or elicit a response that causes an adverse effect or alters the therapeutic effect of the drug. A *clinically-relevant* interaction can be defined as one associated with either toxicity or such a loss of efficacy that warrants the attention of health care professionals.¹

The best information about HDIs comes from case observations (detailed and validated if possible) and clinical studies. Assessment of the risk of an adverse effect from a potential herb-drug interaction considers several factors:^{2,3}

- the quality of the evidence, such as probable or highly probable causality from case reports; confirmation of, and ideally repeated, results from clinical studies with clinically-relevant endpoints⁴
 - A well-documented case report (especially with a positive rechallenge) does not always constitute a lower level of evidence than a negative result from a controlled trial.³ This is provided that all other possible causes have been considered and adequately dealt with – thus “separating interaction from over-reaction”⁴. Generally however, case reports are not considered to provide robust and reliable evidence of herb-drug interactions,⁵ and the poor quality of reporting, such as due to incomplete information, is a continuing limitation.⁶ Case reports very often fail to mention the dose of the herb, whereas clinical studies do, so the intensity of the interaction in case reports may be overestimated.⁷ Causality can be assessed using a validated analytical tool such

as the Drug Interaction Probability Scale (DIPS), which provides a score denoting the interaction as having highly probable, probable, possible or doubtful causation.⁸ See also Note C.

- The quality of the publication should also be considered – a poster from a scientific meeting is regarded as a lower level of evidence than well-documented case reports and controlled trials (due to lack of peer review). Is the pharmacokinetic study placebo-controlled?
- Theoretical concerns based on pharmacological activity in animals or *in vitro* models are considered the lowest quality of evidence and are often speculative at best.
- the incidence of the interaction (what is the chance that the interaction occurs? how many well-documented cases are reported compared to the extent of use of the herb?)
- the seriousness of the potential adverse reaction, for example in order of increasing importance:
 - an insignificant clinical effect from an increased drug level without clinical symptoms or an increase in INR (international normalised ratio)⁹ up to 4.0 in the case of warfarin
 - transient inconvenience (< 2 days) without residual symptoms such as fatigue, nausea
 - failure of therapy for nonserious disease such as decreased effects of an antacid
 - prolonged (> 7 days) or permanent residual symptoms or invalidity such as the toxic effects of digoxin or an increase in INR to greater than 6.0
 - failure of life-saving therapy such as failure of therapy with antiretroviral drugs or cyclosporin
 - death or severe side effects

By considering these factors and the totality of evidence, the risk of a herb-drug interaction causing an adverse effect would range from very low (such as where evidence is poor or lacking and the effect is clinically irrelevant) to contraindicated (such as where the evidence consists of controlled, published interaction studies with a clinically-relevant endpoint, the adverse outcome is clinically very relevant including decreasing the levels of drugs that are being prescribed for serious conditions). An altered plasma drug level in healthy volunteers or even patients without a substantial clinical effect would be considered low or medium risk.

Probe Drugs

Studies using probe drugs, which assess individual cytochrome P450 enzyme activity and hence potential interactions for drugs that utilise that enzyme, are only included in the chart where the drug is currently used clinically. For example, midazolam (a benzodiazepine, used clinically as a sedative and frequently in anaesthesia) is metabolised by CYP3A4 and can be used to assess the interaction of other drugs and herbs with this enzyme (e.g. another drug or herb may inhibit or induce CYP3A4 resulting in increased or decreased plasma drug levels, respectively). A number of drugs are used as probes for CYP3A4 activity such as nifedipine and alprazolam. Other examples of probe drugs included in the chart due to their therapeutic activity include tolbutamide (for CYP2C9 activity), omeprazole (CYP2C19) and talinolol (P-glycoprotein). (P-glycoprotein helps transport molecules across biological membranes and hence can affect the absorption and elimination of a drug.) Although there are a large number of cytochrome P450 enzymes, more than 90% of the metabolism of drugs is due to the activity of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. For a comprehensive review of the effect of herbs on probe drugs in clinical trials the reader is referred to the following systematic review: Kennedy DA, Seely D. *Expert Opin Drug Saf* 2010; **9**(1): 79-124.

Studies ideally need to have administered the herb for at least 7 days and investigated drug exposure by using the area under the plasma/serum concentration-time curve (AUC).

The test used to measure CYP activity also determines how robust the findings. For example, measurement of AUC and C_{max} of the probe drug is more accurate than the metabolic ratio (i.e. ratio of its metabolite to the parent drug),⁵ and in particular, the rapid, but less robust method, single-time point phenotypic metabolic ratios.^{9,10} Urinary metabolic ratios often have a much weaker correlation to CYP enzyme activity and are also not closely correlated to plasma-based results.⁵

HDI Chart Examples: How the Recommended Action is Determined

Contraindicated

St John's Wort and Digoxin

- Three clinical studies (two controlled with placebo) found St John's wort extract high in hyperforin sharply decreased drug levels. The decrease in drug levels increased with increasing doses of St John's wort.

Evidence considered strong and adverse outcome considered serious, in addition to the drug having a narrow therapeutic window (small changes in blood levels may have considerable pharmacological effect).

Dan Shen and Warfarin

- Three case reports of bleeding complications and elevated INRs (above 5.5) were observed and INR returned to normal target range after cessation of herb. Dan shen was the only substance introduced after the INR was initially stabilised.

Reasonably strong case report evidence and adverse effects considered serious.

Bladderwrack and Hyperthyroid Medication, Bugleweed and Thyroid Hormones, Cat's Claw and Immunosuppressant Medication

Although the evidence is based on theoretical concerns only, the adverse effect from the potential interaction is considered great enough for a contraindication.

Monitor (medium level of risk)

St John's Wort and Amitriptyline

- Clinical study (not controlled with placebo) with patients found a decrease in drug levels.

Evidence considered moderate, given the wide use of the herb. Assigned medium rather than low risk due to seriousness of potential adverse outcome.

Garlic and HIV Protease Inhibitors

- Clinical study (not controlled with placebo) with healthy volunteers found an allicin-containing garlic tablet caused marked decrease from baseline in plasma drug concentration.
- Another study also with healthy volunteers taking an allicin-containing garlic tablet, found a minor decrease overall in AUC (15%) with large variability (AUC increased in several volunteers).
- Case reports: virologic failure with suboptimal drug levels confirmed in three patients consuming garlic in the diet.

Evidence considered moderate, as there are very few case reports even though garlic is widely consumed in the diet. Assigned medium rather than low risk due to potential adverse outcome.

Cranberry and Immunosuppressives (Tacrolimus)

- A case of low serum drug level reported. Cessation of cranberry extract returned levels to the desired range. Causality was rated as possible using DIPS.

Evidence not strong with the causality rated only as possible, but assigned medium risk due to the seriousness of potential adverse outcome (rejection in transplant patient).

Monitor (low level of risk)

St John's Wort and Anticonvulsants

- Theoretical concern raised in 2000 by regulators on the basis that St John's wort may induce cytochrome P450, the pathway by which some drugs including anticonvulsants are metabolised, thereby potentially increasing their breakdown and reducing their blood concentrations.
- No effect on carbamazepine pharmacokinetics found in a 2000 clinical study with healthy volunteers (not controlled with placebo).
- One case reported with few details in 2007 in which an increase in the frequency and severity of seizures was reported in a patient taking several anticonvulsants, two of which are not metabolised by cytochrome P450.
- A study published in 2004 found increased excretion of a mephenytoin metabolite in some volunteers – those with a CYP2C19 wild-type genotype (extensive metabolisers). In poor metabolisers (mutant genotype; having a deficiency of CYP2C19 activity) there was no significant alteration. (Mephenytoin is almost exclusively metabolised by CYP2C19.) The clinical significance is unknown, as plasma drug levels of mephenytoin were not measured.

Evidence considered low, with a clinical study supporting a lack of interaction despite the theoretical concern. Due to the recognised ability of St John's wort to interact with some drugs metabolised via cytochrome P450 (particularly CYP3A4), and the importance of maintaining stable blood levels of anticonvulsants this interaction was assigned low rather than very low risk. The case report does not support the theoretical concern (different metabolism). Additional and well-documented case reports would be required to alter the risk assessment.

Ginkgo and Hypoglycaemic drugs (Tolbutamide)

- Clinical study with healthy volunteers found a high dose of Ginkgo (50:1 extract: 360 mg/day, equivalent to 18 g/day of dried leaf) decreased the area under concentration versus time curve by 16% (statistically significant but being less than a 20% decrease is not regarded as clinically significant). No statistically significant differences found for other pharmacokinetic parameters.
- To assess the effect on the pharmacodynamics of tolbutamide, volunteers were also given a 75-g oral dose of glucose. When combined with Ginkgo the blood glucose lowering effect of tolbutamide was less than with tolbutamide alone, but the difference was not even statistically significant.

The decrease in exposure to tolbutamide caused by a high dose of Ginkgo did not have a significant effect on the ability of tolbutamide to lower glucose in healthy volunteers. Assigned low risk until information in diabetic patients becomes available.

Withania and Thyroxine

- Case report where ingestion of Withania resulted in increased serum T4 level.
- Clinical study found Withania improved serum T4 level in subclinical hypothyroid patients.
- Observation of three patients within a clinical study, which administered an extract of Withania (*root and leaf*) and relatively high doses of withanolides: increases in serum T4 from baseline, although one had subclinical hypothyroidism.
- Placebo-controlled study with healthy volunteers found no significant effect on thyroid hormones.

No case reports or clinical studies involving intake of the herb and the drug, so the concern is based solely on the ability of Withania root to stimulate thyroid hormones, particularly in patients with low thyroid function.

Monitor (very low level of risk)

Siberian Ginseng and Digoxin

- One case report: possibly increased plasma concentration of drug but ECG (electrocardiogram) unchanged. The possibility that the herb may have interfered with the digoxin measurement was also raised, and later supported.
- No effect on plasma concentration of drug in later controlled clinical trial.

The case report provides minimal evidence, with a lack of clinical relevance (ECG results) and the possibility of testing interference. The clinical trial results reduce the strength of evidence.

Devil's Claw and Warfarin

- One poorly documented case report. Subsequently causality was rated as doubtful using DIPS.

Minimal evidence with too few details. No other evidence exists to suggest this interaction.

Notes

A. An example of a clinically-relevant endpoint is the increase in serum LDL cholesterol caused by St John's wort in patients taking atorvastatin. In the absence of trials using clinical endpoints how then is the risk assessed? The pharmacokinetics and/or pharmacodynamics are considered,⁹ but how much of a pharmacokinetic change should be considered clinically relevant? This issue, in the context of drug-drug interactions, is a topic for debate.¹¹ Tests of statistical significance such as the p value on parameters such as the peak plasma concentration are not necessarily clinically relevant.^{12,13}

In interaction trials where clinically-relevant endpoints have not been measured, the US Food and Drug Administration has provided *guidelines* to assess the relevance of the pharmacokinetic results. A decrease of 20% up to an increase of 25% in drug exposure (e.g. peak plasma concentration, AUC) does not result in relevant changes of drug effect and no clinically-significant interaction is present. (Technically, the 90% confidence interval for the geometric mean ratio of the herb-drug phase to the drug phase needs to be within 0.8–1.25.)¹² This limit has been considered too conservative, with a recommendation that the no-effect limit be expanded to ranging from a decrease of 30% up to an increase of 43% in drug exposure (i.e. the ratio falls within 0.7–1.43).¹⁴ The FDA no-effect limit does not constitute a hard and fast rule however as, for example, the therapeutic index of the drug should still be considered.¹⁵ (For example, for drugs with a narrow therapeutic range, the 90% confidence interval for AUC ratio should be contained within tighter confidence limits (0.9–1.12).¹⁶) Not all clinical studies however provide the information to assess the no-effect limit.

B. A herb-drug interaction can have:

- a pharmacodynamic basis such as similar or opposing pharmacological effects, such as the effect on INR (international normalised ratio), and/or
- a pharmacokinetic basis (making the drug more or less available to the body).

C. Another validated tool is the Roussel Uclaf Causality Assessment Method (RUCAM), which assesses causality where drug- or herb-induced liver injury is suspected. This tool provides a score denoting causality as highly probable, probable, possible, unlikely or excluded. RUCAM assesses cases where liver injury is suspected from the intake of one or more drugs (known as a drug-induced liver injury), or less frequently, a herb (herb-induced liver injury), but is also relevant if the liver injury or other adverse effect is caused by the combination of herb and drug.

D. The target therapeutic range for oral anticoagulation is an INR (international normalised ratio) between 2.5 and 3.0 depending on the condition. A rise in INR increases the risk of bleeding (for example, when INR is well above 5.0). A decrease in INR is also considered undesirable as a low INR may increase the risk of clotting.

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