MEDI HERB

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 normalized 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 report long-term use of laxative herbs or potassium-depleting diuretics.
- Critical drugs should be taken at different times of the day from herbs (and food) to reduce chemical or pharmacokinetic interactions. They should be separated by at least 1 hour, preferably more.
- Stop all herbs approximately 1 week before surgery. Milk thistle may help reduce the toxic after-effects of anesthetic drugs, so it can be taken up to the day before, and then again, after surgery.
- Carefully monitor the effects of drugs such as antihypertensives and antidiabetic drugs when combining with herbal remedies. The herbs may make them more or less effective. In the ideal situation the dose of the drug could be adjusted.
- Interactions may be dose related for the herb and the drug, for example, St John's Wort and digoxin.
- The use of antioxidants (including herbs) in conjunction with chemotherapy and radiotherapy for cancer is controversial. 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 endpoints[A]
  - **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 normalized ratio)[c] 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 utilize 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 anesthesia) is metabolized 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 Cmax 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).

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 metabolized, 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 metabolized 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 metabolizers). In poor metabolizers (mutant genotype; having a deficiency of CYP2C19 activity) there was no significant alteration. (Mephenytoin is almost exclusively metabolized 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 recognized ability of St John's Wort to interact with some drugs metabolized 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 Hypoglycemic drugs (Tolbutamide)

- Clinical study with healthy volunteers found a high dose of Ginkgo (50:1 extract: 360 mg/day) 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.

Monitor (low level of risk)

Ashwagandha and Thyroxine

- Case report where ingestion of Ashwagandha resulted in increased serum T4 level.
- Clinical study found Ashwagandha improved serum T4 level in subclinical hypothyroid patients.
- Observation of three patients within a clinical study, which administered an extract of Ashwagandha (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 Ashwagandha root to stimulate thyroid hormones, particularly in patients with low thyroid function.

Monitor (very low level of risk)

Eleuthero 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.

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,[B] 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 normalized 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 normalized 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.

References

1 Scheife RT, Hines LE, Boyce RD et al. Drug Saf 2015; **38**(2): 197-206

2 Mills S, Bone K (eds). *The Essential Guide to Herbal Safety.* Churchill Livingstone, USA, 2005, pp 50-88.

3 De Smet PA. *Br J Clin Pharmacol* 2007; **63**(3): 258-267

4 Coxeter PD, McLachlan AJ, Duke CC et al. *Curr Med Chem* 2004; **11**(11): 1513-1525

5 Hermann R, von Richter O. *Planta Med* 2012; **78**(13): 1458-1477

6 Mazhar H, Foster BC, Necyk C et al. *J Child Adolesc Psychopharmacol* 2020; **30**(1): 38-47

7 Ge B, Zhang Z, Zuo Z. *Evid Based Complement Alternat Med* 2014; **2014**: 957362

8 Awortwe C, Makiwane M, Reuter H et al. *Br J Clin Pharmacol* 2018; **84**(4): 679-693

9 Gurley BJ, Gardner SF, Hubbard MA et al. *Clin Pharmacol Ther* 2002; **72**(3): 276-287

10 Malati CY, Robertson SM, Hunt JD et al. *J Clin Pharmacol* 2012; **52**(6): 932-939

11 Fuhr U. *Eur J Clin Pharmacol* 2007; **63**(10): 897-899

12 Guidance for Industry: Drug interaction studies: study design, data analysis and implications for dosing and labeling. Draft published September 2006. Available from www.fda.gov/cder/guidance/6695dft.pdf. Accessed October 2008.

13 Greenblatt DJ. *Cardiovasc Ther* 2009; **27**(4): 226-229

14 Mueller SC, Majcher-Peszynska J, Mundkowski RG et al. *Eur J Clin Pharmacol* 2009; **65**(1): 81-87

15 Butterweck V, Derendorf H. *Clin Pharmacokinet* 2008; **47**(6): 383-397

16 Canadian Agency for Drugs and Technologies in Health. *What are Bioavailability and Bioequivalence?* CADTH, 2012. Available online: http://www.cadth.ca/media/pdf/Generic_prof_supplement_en.pdf. Accessed August 2013.

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

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).

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 Hypoglycemic 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, standardized 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*.

Potential Herb-Drug Interactions for Commonly Used Herbs*

Drug	Potential Interaction	Basis of Concern	Recommended Action
Boswellia *Boswellia serrata*			
Warfarin	May increase effectiveness of drug.	Two case reports (increased INR; concentrated extract (95%; 1.2–1.5 g/day), causality rated as probable (score 6)[B]).[1]	**Monitor** (low level of risk).
Gotu Kola *Centella asiatica*			
Central nervous system (CNS) depressants, GABAergic drugs, sedatives, benzodiazepines	May increase effects of drug.	Gotu Kola may increase cerebral levels of GABA, and the sedative actions may increase the risk of sedation when combined with these CNS depressants. Drowsiness has been reported, particularly in high doses. Monitor patient for increased sedative effects.	**Monitor** (low level of risk).
Turmeric[YY] *Curcuma longa*			
Antineoplastics/ Chemotherapeutics	May decrease effectiveness of drug.	Turmeric is known to stimulate Nrf2/ARE and exert an antioxidant action. Antioxidant and Nrf2 herbs may inhibit the action of chemotherapeutic drugs that work via oxidation. Therefore, caution is advised regarding co-prescription of Turmeric with chemotherapeutic agents.	**Monitor** Separate 48 hours before and after cytotoxic or chemotherapeutic treatment.
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.[2] **Herb with Drug** Case report (increased INR in a patient taking a "Turmeric containing product" and warfarin); few details provided.[3] Case report (gastrointestinal bleeding in a patient taking clopidogrel); few details provided; survey and review of medical file of hospitalized patient, although causality rated as probable (score 5)[B].[4]	**Monitor** (low level of risk).
Ciclosporin	May increase drug levels.	Turmeric may increase serum levels of ciclosporin by inhibiting drug metabolism and bioavailability (via CYP3A4), which could increase the risk of toxic effects from the medication.	**Monitor (**medium level of risk).
Drugs metabolized by CYP2D6, CYP3A4 and/or P-glycoprotein with a narrow therapeutic window	May increase drug levels.	Human clinical evidence demonstrates Turmeric inhibits the clearance of drugs metabolised by CYP2D6, 3A410 and P-glycoprotein, and curcumin inhibits CYP1A2. This may increase the serum levels of certain medications and therefore increase the risk of toxicity. Curcumin can also significantly reduce drug efficacy of CYP2A6 substrates via induction of the enzyme. These alterations in drug levels are particularly relevant to medications with a narrow therapeutic index (NTI). Therefore, consider risk to benefit; if using, separate doses by as many hours as possible (depending on half-life of the drug), and monitor for changes to drug efficacy.	**Monitor** Separate doses; monitor increased medication efficacy/toxicity.
Etoricoxib	May potentiate adverse hepatic effect of drug.	Case report of acute liver injury (long-term use of herb).[5]	**Monitor** (low level of risk).
Sulfasalazine	May increase drug levels.	Human evidence suggests a potential medication interaction between Turmeric and sulfasalazine, particularly in patients with specific genotypes, although the evidence is mixed, with other research demonstrating Turmeric may be beneficial for patients with conditions like ulcerative colitis (UC) when used alongside sulfasalazine. It appears a small subsection of the population may be more susceptible to this interaction, therefore while studies show Turmeric may be beneficial for UC, patients should be monitored for changes to sulfasalazine efficacy and/or toxicity.	**Monitor** for increased levels and side effects of drugs.
Tacrolimus	May increase drug levels.	Case reports: nephrotoxicity in liver transplant patient; high dose with food, estimated at "15+ spoonfuls daily" starting roughly 10 days prior to rehospitalization[6] (causality rated as probable (score 7)[B]);[7] elevated drug level in transplant patient (meal containing a lot of turmeric).[8]	**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).[9]	**Monitor** at high doses (≥ 300 mg/day curcumin, low level of risk).

REFERENCES

Braun L. *Herb Drug Interaction Guide for Pharmacists*. FH Faulding, August 2000; Fugh-Berman A. *Lancet* 2000; **355**(9198): 134-138

1 Paoletti A, Gallo E, Benemei S et al. *Evid Based Complement Alternat Med* 2011; **2011**: 612150

2 Fung FY, Wong WH, Ang SK et al. *Phytomedicine* 2017; **32**: 88-96

3 Medsafe Monitoring Communication. Beware turmeric/ curcumin containing products can interact with warfarin, 30 April 2018. Available from: http://www.medsafe.govt.nz/safety/EWS/2018/Turmeric.asp. Accessed May 17, 2021.

4 Levy I, Attias S, Ben-Arye E et al. *Br J Clin Pharmacol* 2017; **83**(4): 836-845

5 528- Fernández-Aceñero MJ, Ortega Medina L, Maroto M. *J Clin Exp Hepatol* 2019; **9**(3): 409-411

6 Nayeri A, Wu S, Adams E et al. *Transplant Proc* 2017; **49**(1): 198-200

7 Awortwe C, Makiwane M, Reuter H et al. *Br J Clin Pharmacol* 2018; **84**(4): 679-693 [this reference was moved up]

8 530- [No authors listed]. *Lakartidningen* 2010; **107**(18): 1238

9 531- Juan H, Terhaag B, Cong Z et al. *Eur J Clin Pharmacol* 2007; **63**(7): 663-668