



# Combining herbs and drugs – at times a fractious marriage

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For some time now, the therapeutic use of herbs has been expanding<sup>1</sup>. For many people, such as those suffering from chronic disorders, or the elderly, herbal medicine seriously challenges the previous dominance of conventional drugs.

***Certain herbs used simultaneously may counteract, mimic or magnify the effect of some conventional drugs***

In addition, there are many people who decide on their own initiative to take herbs in combination with prescribed drugs for their particular condition. The person may find this completely satisfactory, with evident subjective improvement; however, it could happen that the drug and the herb interact together, and this could lead

to either a different, unwanted therapeutic response, or even to experiencing an unsettling toxic effect.

Perhaps the original indication that an herbal product could interact significantly with drug action appeared more than 20 years ago<sup>2</sup>. It was observed that if a patient who had undergone kidney transplantation drank freshly prepared grapefruit juice, then the metabolism of the immunosuppressant ciclosporin was markedly reduced. This allowed the dose to be reduced, with valuable benefits regarding tolerance and cost-benefit. We now know that the metabolic enzymes (comprising the *cytochrome P450 system*) of the patient's liver were being inhibited by something in the grapefruit juice, so that higher levels of the active drug persisted for longer. As a result, a lower dose of the drug could be employed, without compromising clinical efficacy or outcome.

If grapefruit has an important effect – why not herbs? Numerous clinical trials, case studies and anecdotal case reports have emerged which confirm the undoubted interaction of herbs with drugs<sup>3</sup>.

***Some drugs can interact with food – MAO- inhibitors and cheese; antibiotics and milk; warfarin and green vegetables***

This is not unexpected; if a herb is capable of triggering a pharmacological response, then it could conceivably interfere, to a greater or lesser extent, with a conventional drug's desired activity. This has important implications in day-to-day practical healthcare, as many people are taking not one, but several, potent drugs. The potential for herb-drug interactions, and the attached risks, is therefore immense at a time when herbal products are reaching a broader public.

A number of popular herbs – garlic, ginkgo and ginseng amongst them – have been shown over the last few years to interact with specific conventional drugs<sup>4</sup>. Some of the interactions are of minor significance, and do not pose a real problem. Others interactions, however, are more serious, and do urge caution.

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The interaction of herbs with drugs appears to be highly selective<sup>5</sup>. That is, an interaction is only significant or clinically important if a critical aspect of the drug's pharmacological action is interfered with. For example, if a herb affects a drug's rate of absorption into the body, it will only create problems and so upset the therapeutic benefits if it is important for the drug to be absorbed quickly (as with *analgesics*), or totally (as with *antibiotics*). If the absorption rate is not a critical factor (as with *antidepressants* or *anxiolytics*) then the effect of the herb on the drug is not likely to be important.

## **Let us examine some specific examples of herb-drug interactions.**

The widely used culinary and therapeutic herb garlic is known to decrease absorption of the antiretroviral agent saquinovir, and is implicated in the onset of hypoglycaemia in diabetic patients taking chlopropamide, presumably

**Licorice increases the plasma levels of prednisolone – the anti-allergic and anti-inflammatory steroid drug**

**Interaction works both ways: herbs can interact with drugs, but drugs can also interact with herbs.**

because of its intrinsic effect in lowering blood glucose levels<sup>6</sup>. Another very popular herb, ginkgo increases clotting time in patients taking aspirin or warfarin, and is implicated in increasing blood pressure in hypertensive patients taking a thiazide diuretic. Ginseng, a herb which is increasingly sought after, also interferes with warfarin activity, digoxin levels and certain antidepressants. The increasingly widely used St John's wort is linked to a whole range of drug interactions, beyond those mentioned immediately above – a number of anxiolytics, lipid lowering agents, immunosuppressants, anti-retrovirals, anti-diabetic agents, oral contraceptives, and others.

The relevance of the herb-drug interaction is determined by (a) the degree of interaction; (b) the extent of the interaction in people using the two; and (c) the seriousness of the adverse effect. For instance, hypericum is now linked to breakthrough bleeding and unwanted pregnancies in women taking certain oral contraceptives, so this is an important interaction, with possibly serious implications. In this situation, the use of the herbal product should only be taken for good reason, supported by patient counseling, and with alternative contraception adopted. This constraint equally applies to Parkinson's disease patients being treated with L-dopa. If the herb kava is taken simultaneously, the patient runs the risk increases of treatment failure brought about by the drug.

The impact of an herb interfering with the action of a conventional drug can be particularly serious when the drug has a narrow therapeutic index. This means that if the drug concentration in the body for therapeutic effect is close to the toxic concentration, then a slight change in level brought about by the drug can either adversely reduce the therapeutic effect, or bring on side effects.

## **Not all herb-drug interactions are unwelcome or deleterious.**

We have already seen that a component of grapefruit juice inhibits ciclosporin metabolism, so allowing for a lower dose, without compromising the clinical outcome in organ transplantation. The herb angelica also has a similar effect. Another example is piperine<sup>7</sup> (an active ingredient of peppers), which increases the bio-availabilities of the anti-epileptic drug phenytoin, the beta blocker propranolol, and the bronchodilator theophylline. In patients with pulmonary tuberculosis, ginseng increases rifampicin blood levels.

Regarding drug toxicity, huangqin is effective in ameliorating the digestive problems associated with irinotecan in patients with cancer.

## **How do herb-drug interactions occur?**

For most herb-drug interactions, the mechanisms are unknown. What we do know, however, is that a herb does not combine chemically with the drug to form a toxic agent<sup>8</sup>. In most cases, changes to drug absorption, or its metabolism

**Reducing or eliminating either drug or herb is a clinical decision, based upon perceived relative value of both forms**

in the body, or its clearance from the system brought about by the herb plays a pivotal role. Indeed, we do know that many herbs can induce or inhibit drug metabolising enzymes located in the liver and intestinal tract. These enzymes, which are mainly of the cytochrome P450 type, are made less effective, so the net effect is raised blood drug concentrations and reduced clearance of the drug (and metabolites) from the body<sup>9</sup>.

Alternatively, some herbal components may act on the same tissue receptors or enzymes which are targeted by a particular drug. This is understandable, as many conventional drugs are in fact derived from natural herbal products. This could theoretically result in either *drug antagonism*, or in *drug synergism*. The former may lead to a toxic response, whilst the latter to a lack of satisfactory drug action<sup>10</sup>.

The ways an herbal product interferes with the drug's pharmacological action can be allocated to either *pharmacokinetic* and or *pharmacodynamic* interactions.

### ***Pharmacokinetic interaction***

**(a) Inhibition of absorption.** The herb or drug acts on the other active agent to reduce or minimise its absorption. A number of agents have been identified:

- Pectins, resins, tannins may bind to certain antibiotics, preventing unimpeded absorption of drug.
- Garlic interacts with several drugs. It also reduces plasma concentrations of chlorzoxazone.
- Ginkgo decreases the plasma concentrations of many drugs.

Avoidance of this interaction: *separate timing of drug and herb administration.*

**(b) Enhancement of absorption.** This is usually the result of increased gastric emptying or shorter gut transit time.

- Laxatives can increase these processes.
- Certain saponins can increase gastric emptying, so enhancing the rate of gastric emptying.

Avoidance of this interaction: *reduce laxative usage / alternate times / divide dosing between morning and evening*

**(c) Binding of drug by herb component.** Some antibiotics are chemically bound to certain botanical substances. This prevents or inhibits absorption through the intestinal wall, as the drug; herb complex is either too big to absorb, or too poorly soluble in the intestinal fluid.

Avoidance of this interaction: *Separate the timing of dosing of the drug and the herbal product.*

**(d) Drug metabolism increased.** The herbal product promotes an increase in metabolic enzymes in the liver, so boosting the breakdown or elimination of drugs.

- Grapefruit juice decreases metabolism of ciclosporin and other drugs, due to induction of liver metabolic CYP450 enzyme
- Echinacea affects the metabolic clearance of caffeine and certain anti-anxiety drugs.
- St John's wort reduces the plasma concentrations and increases clearance of a wide range of drugs.
- Ginkgo decreases the plasma concentrations of many drugs.

Avoidance of this interaction: *monitor plasma drug levels, and adjust dosage to compensate.*

### ***Pharmacodynamic interaction***

**(a) Electrolyte depletion.** Laxatives and diuretic drugs can reduce sodium, potassium levels in the body, and so lead to adverse cardiac effects<sup>11</sup>. Herbs with laxative, purgative and diuretic effects should not be used with, for example, cardiac drugs: the risk is too high.

Avoidance of this interaction: Separate the timing of dosing of the drug and the herbal product.

**(b) The pharmacological effect is intensified.** Certain herbs have specific pharmacological effects. If a drug being co-administered, then an additive or perhaps synergistic effect can arise.

- Several herbal products and certain drugs may have the same effect on blood clotting mechanisms.
- Hypoglycaemic drugs and herbal products use to treat diabetes may act together.
- Herbs which contain the alkaloids caffeine and ephedrine, or similar, may increase nerve stimulant drug action.
- St John's wort may enhance the nervous system effects of certain antidepressant drugs.

Avoidance of the interaction: if both drug and herb are being used for the same therapeutic objective, then a decision has to be made for the preference of one active agent based on cost, side effects and long term effects.

**(a) Drug effect is opposed by herbal action.** Drugs which act as inhibitors, like beta blockers and proton pump inhibitors may have their action opposed by certain herbal products. As a result, the desired action is negated.

- St John's wort inhibits the uptake of serotonin and other monoamines, so can interfere with several anti-depressants and anti-Parkinson's drugs.

Avoidance of this interaction: Review the need for both types of therapy, and decide on one. Alternatively, administer the herbal product with a substantial interval between.

## **Conclusion**

There are a significant number of people who take herbs in addition to their prescribed conventional medicines. Unfortunately, many drugs interact with herbal medicines, and *vice versa*. This situation is analogous to the drug-drug interaction that is now well established and documented. Complications can arise because the clinical importance of herb-drug interactions depends on many factors associated with the particular herb, drug and patient.

An herb-drug interaction could, and occasionally does, lead to serious clinical consequences, so the consumer should be made aware of this, and take the necessary precautions<sup>12</sup>. As herbal therapy is slowly but surely being regarded as an integrated part of medical treatment, not merely as junior or second-best alternative medicine based purely on experience and tradition, better understanding of any herb-drug interactions can have a very positive influence on the acceptance of herbal therapy generally.

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## Further information

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