The hidden problem of herb-drug interactions

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Potentially harmful interactions between herbs and prescription medicines are common, yet healthcare professionals often do not ask about herbal remedies when prescribing and patients do not volunteer that they are taking them. This article discusses the types of herb-drug interaction that can occur and how they can be recognised and avoided.

We have used herbs for millennia, probably even before we were recognisably Homo sapiens. Dogs, deer, bears, elk, great apes and, possibly, your next patient all seem to deliberately use medicinal plants to self-medicate. Even in these days of pharmacologically sophisticated drugs, herbal remedies remain popular.

Quite how popular is not clear, however: UK studies suggest that between 13 and 44 per cent of adults use herbal remedies. An audit of 100 acute medical emergency admissions to a Liverpool hospital found that 24 per cent took herbal medications. Most of these (83 per cent) took the herb concomitantly with at least one prescription medication. The herb’s use was, however, noted on just one patient record.2 “The literature gives widely varying estimates of the extent of herbal use, because of differences in the way investigators capture data and ask whether people take herbal medicines,” says Professor Sir Munir Pirmohamed, who holds the David Weatherall chair of medicine at Liverpool University and who was one of the audit’s authors. “Nevertheless, it’s clear that interactions between herbs and prescription medicines are common, but under-recognised.”

Indeed, certain prescription medicines can have potentially serious interactions with several herbs (see Table 1). “The most important interactions vary according to the type of study and area of medicine,” Professor Pirmohamed remarks. “St John’s wort, however, remains a common and important interaction, despite the warnings that are on boxes and increased awareness.”
For instance, St John’s wort (Hypericum perforatum) increases levels of the neurotransmitter serotonin. So, combining St John’s wort and other serotonergic agents – such as SSRIs – can trigger the potentially fatal serotonin syndrome. St John’s wort can also interact with oral contraceptives leading to unplanned pregnancies and breakthrough bleeding. Yet while some potentially significant interactions are clear, pharmacologists are a long way from fully understanding the risks.

Types of interaction
Pharmacologists recognise three broad types of drug interaction: pharmaceutical incompatibility, pharmacodynamic and pharmacokinetic interactions. Pharmaceutical incompatibility refers to the complexes that form when certain drugs are mixed. This interaction underlies therapeutic chelation, such as using desferrioxamine to treat iron poisoning.

Pharmacodynamic interactions arise when the concomitant agents have similar or opposite pharmacological effects. For example, concomitant ethanol can potentiate the sedative effects of benzodiazepines or the histamine H1-receptor antagonists used to alleviate travel sickness.6 In European and Asian traditions, motherwort (Leonurus cardiaca) is used for, among other ailments, ‘cardiac debility’, tachycardia, anxiety, insomnia, and amenorrhoea. Motherwort is a sedative. With concomitant benzodiazepines, motherwort can have a synergistic sedative effect that could result in a coma. The increase in serotonin levels with St John’s wort for a variety of other ailments including sleep disorders, the common cold, herpes, HIV infection, as a topical analgesic, and as an enema for ulcerative colitis. However, St John’s wort potentially reduces the concentration or effect of several drugs including warfarin, ciclosporin, HIV protease inhibitors, theophylline, digoxin and oral contraceptives. These interactions probably occur as a result of induction of the cytochrome P450 isoenzymes, such as CYP3A4, CYP2C9 and CYP1A2.3

P-glycoprotein is responsible for other interactions between herbs and prescription medicines. This transmembrane transporter, which is vital for the elimination, absorption or both of many drugs, is extensively expressed by the intestinal epithelium, hepatocytes, renal proximal tubular cells, the adrenal gland and the blood-brain barrier.

<table>
<thead>
<tr>
<th>Herb</th>
<th>Example of concomitant medicine</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>Alfalfa</td>
<td>Warfarin</td>
<td>Increased bleeding risk</td>
</tr>
<tr>
<td>Capsicum</td>
<td>ACE inhibitors</td>
<td>Increased absorption</td>
</tr>
<tr>
<td></td>
<td>Monoamine oxidase inhibitors</td>
<td>Increased blood pressure</td>
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<tr>
<td>Echinacea</td>
<td>Benzodiazepines</td>
<td>Increased plasma concentrations</td>
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<tr>
<td></td>
<td>Ciclosporin</td>
<td>Immune stimulation</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>Warfarin</td>
<td>Increased bleeding risk</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Anticoagulants</td>
<td>Increased bleeding risk</td>
</tr>
<tr>
<td>Garlic</td>
<td>Anticoagulants (including warfarin) Immunosuppressants</td>
<td>Increased bleeding risk Reduced effectiveness</td>
</tr>
<tr>
<td>Ginger</td>
<td>Anticoagulants (including warfarin) H2-receptor antagonists and proton-pump inhibitors Hypoglycaemic drugs</td>
<td>Increased bleeding risk Increased gastric acid production Reduced blood sugar</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Anticoagulants Antipsychotics Aspirin and COX-2 inhibitors</td>
<td>Increased bleeding risk Possible seizure induction Increased bleeding risk</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Hypoglycaemics Warfarin</td>
<td>Reduced blood sugar Reduced effectiveness</td>
</tr>
<tr>
<td>Green tea</td>
<td>Warfarin</td>
<td>Reduced effect (contains vitamin K)</td>
</tr>
<tr>
<td>St John’s wort</td>
<td>Ciclosporin Digoxin HIV protease inhibitors (eg indinavir) Oral contraceptives SSRIs and triptans Warfarin</td>
<td>Reduced levels by 25–62%; increased risk of rejection Reduced concentrations Reduced levels by 49–99% Breakthrough bleeding and unplanned pregnancy Increased serotonin concentrations Unstable, usually reduced, international normalised ratio (INR)</td>
</tr>
</tbody>
</table>

Table 1. Examples of interactions between conventional medications and herbs.4,6
St John’s wort (Hypericum perforatum) is associated with several important drug interactions

P-glycoprotein transports, for example, the immunosuppressant ciclosporin. St John’s wort can induce P-glycoprotein. So, the combination of induction of CYP3A4 (which metabolises ciclosporin) and P-glycoprotein can reduce plasma levels of ciclosporin by between 25 and 62 per cent within three to four weeks of starting St John’s wort. In some cases, concomitant St John’s wort can reduce ciclosporin concentrations to subtherapeutic levels, increasing the risk that the patient will reject a transplanted organ.3

Professor Pirmohamed notes that understanding the role of P450 enzymes, phase II enzymes and transporters “is always important” when prescribing any drug. (As an aside: phase II metabolism occurs when metabolism by cytochrome P450 and the other phase I reactions either do not clear the drug or generate a reactive metabolite. Phase II involves “conjugation reactions”; in other words, enzymes add a large polar group, such as glucuronide, to the drug. This further increases solubility, which aids elimination.)

“Although our understanding of cytochrome P450 and phase II enzymes is good and increasing, that of transporters is much less,” Professor Pirmohamed says. “There are myriad transporters beyond P-glycoprotein that are responsible for the influx of drugs into cells and their efflux out of cells. We do not fully understand the substrate specificities, how transporters vary, and how genetics affects their activity. For herbs, this is complicated by the fact that we do not have enough knowledge of their interaction with P450s, transporters, etc. Therefore, at present it is difficult to predict their interactions.”

**Finding the culprit**

To complicate matters further, isolating the chemicals in the herb responsible for the benefits, risks and interactions is time consuming. St John’s wort, for example, contains at least nine groups of compounds that may contribute to its pharmacological effect.3 Levels may also vary according to where the plant grows and the time of year. Despite its legendary toxicity, yew is used in some medical traditions, such as in parts of northern India, Pakistan and Nepal. With the exception of the aril (the fleshy red seed cover), yew, whether fresh or dried, contains a group of cardiotoxins called taxines. Levels of taxines peak during the winter.8,9

Herbalists believe that various chemicals in a plant act together to increase effectiveness – so-called synergy. Some components, herbalists contend, work together to reduce the risk of side-effects; an effect known as buffering. So herbalists often use several plants together.10 For example, the traditional Chinese herbal remedies Jia Wei Xiao Yao San and Chai Hu Shu Gan Tang, which seem to prolong survival in people with liver cancer when used alongside conventional treatments, contain 10 and seven plants respectively.11

“Herbs contain numerous biologically active substances, but there is also batch-to-batch variation, which makes it difficult to understand mechanisms,” Professor Pirmohamed tells Prescriber. “However, if there is clinical evidence of an interaction, or if it can be surmised from the known activities of the herbal compounds, it is still possible to understand the pharmacology.” Individually, for example, garlic, feverfew and ginseng all modestly inhibit platelet aggregation. In combination, they may have had a significant effect on platelet function. In one case, the interaction between the herbs contributed to an admission for bleeding from an inflamed oesophagus.2

Moreover, pharmacologists increasingly recognise the limitations of interaction studies, which have important implications for the use of conventional drugs. Most interactions studies involve two drugs, usually in healthy volunteers. But patients often receive several drugs and have a range of diseases, some of which may influence metabolic capacity. Inflammation, for example, reduces levels of CYP3A4/5, CYP2C9 and CYP1A2, but increases levels of CYP2E1. Many patients are elderly and levels of several cytochrome P450 enzymes, including CYP3A4/5, CYP2C9 and CYP1A2, increase with advancing age.7

Meanwhile, polymorphisms in the genes encoding cytochrome P450 and other metabolic enzymes can dramatically influence the pharmacodynamics of several drugs. Numerous environmental factors also influence cytochrome P450 levels. For example, in mice at least, differences in the microbiome (see below) can alter expression of more than 100 genes in the liver, including those encoding cytochrome P450. Yet such factors are poorly understood and rarely considered in interaction studies.

“As our population ages, and patients survive with multiple co-morbidities and are on multiple drugs, then the likelihood of interactions is going to increase,” Professor Pirmohamed says. “Although we test for interactions in early phase studies, these are often done in healthy volunteers, who may be poor proxies for elderly patients, who are at highest risk. Thus, an interaction that may not be evident in a young person may suddenly become quite serious in an elderly person with multiple diseases on multiple drugs. The challenge for us is to start thinking about how we can detect and predict these types of interactions: it would be impossible to undertake specific studies as every elderly patient is different.”
The microbiome: another layer of complexity

Recent advances in pharmacologists’ understanding of the mechanisms underlying drug interactions adds another layer of complexity to this common problem. The gut microbiome, for example, consists of some 100 trillion cells from thousands of different species including bacteria, fungi, protozoa and viruses. Indeed, there are 10 cells in the microbiome for every cell in the human body. The microbiome is essential for health and wellbeing. Bacteria in the gut break down otherwise indigestible plant fibre,12 which could have implications for herbal interactions. Other members of the microbiome synthesise essential vitamins and amino acids, aid the development and maintenance of the immune system, and detoxify drugs and other foreign material.12

In the late 1930s, for example, researchers reported that the sulfonamide antibiotic prontosil did not seem to be effective in vitro, but was a broad-spectrum antibacterial in vivo. Researchers resolved the paradox when they found that bacteria in the gut activated prontosil. Today, researchers have identified at least 50 drugs metabolised by the gut microbiota – according to in vitro or in vivo studies or both – although this is almost certainly an underestimate.12

Variations in the microbiome can contribute to the efficiency and tolerability of drugs. For instance, gut bacteria activate sulfasalazine, used for ulcerative colitis and rheumatoid arthritis. Gut bacteria also inactivate 5-aminosalicylic acid, sulfasalazine’s active metabolite. Levels of the bacterial enzymes responsible for the inactivation can vary up to 10-fold between individuals.12 “Metabolism by the gut microbiome is likely to be important for many prescription drugs as well as herbs,” Professor Pirmohamed says. “However, this is a vast area that, even for prescription drugs, is not yet well studied.”

Ask patients about herbal remedies

While there is unequivocal evidence of potentially harmful interactions between some herbs and certain prescription medicines, many probably go unrecognised, Professor Pirmohamed notes. In the Liverpool audit, for example, 46 per cent of the people using herbal treatments were using a preparation with known side-effects or documented interactions.2 “Given the risks and the widespread use, it is vital to ask patients about their use of herbal remedies while taking a routine drug history,” Professor Pirmohamed concludes. “Healthcare professionals do not often ask about herbal remedies and, I suspect, are also not generally aware of the potential for interactions. Patients also do not volunteer that they are taking herbalals as they do not regard them as medicines. Patients regard herbs as being safe. Education of both healthcare professionals and the public is important."

References