INTERACTIONS BETWEEN HERBAL AND CONVENTIONAL MEDICINES: THE ROLE OF CYTOCHROME P450 ENZYMES AND P-GLYCOPROTEIN

Elizabeth M Williamson

The School of Pharmacy, University of Reading, Whiteknights RG6 6AP, U.K.

Summary

The extent of herb-drug interactions (H-DIs) is still largely unknown, although the use of herbal medicines among the general public is increasing. The theoretical and clinical evidence for some important H-DIs is presented, together with an explanation of pharmacodynamic interactions and pharmacokinetic effects involving P-glycoprotein and cytochrome P450 enzymes. Currently, research is being undertaken to identify potential interaction problems by means of *in vitro* and *in vivo* experimental methods; these, together with the most important H-DI's are summarised.

Key words: herb-drug interactions; herbal medicines, cytochrome P450, P-glycoprotein

Introduction

Extent of usage of herbal medicines and herb-drug interactions

The use of herbal medicinal products (HMP's) among the general public is increasing, and it has been estimated recently that in the US, 24% regularly take herbal medicinal products (HMPs) [1,2]. Another report suggests that 16%, or 15 million adults (including 3 million aged 65 or over), took both herbal and prescription medicines at the same time in 2002; even in children, it was found that 29.5% had used complementary or alternative medicine (CAM), and that 12.8% had been given HMP's prior to surgery [3]. Kuo et al [4] in 2004 showed that almost half (46%) of the respondents in a survey were taking herbal medicines concurrently with conventional therapy. In the UK alone it has been reported that 20% of the general population used CAM in the course of a year [5]. However, the true extent of the incidence and significance of herb-drug interactions (H-DI's) is still largely unknown, because unlicensed 'medicines' are rarely prescribed by qualified clinicians, and it is only recently that schemes have been launched to encourage doctors or pharmacists to report adverse reactions to herbal medicines and herb-drug interactions. Patients take herbal remedies in combination with other remedies, for varying durations and at non-standard doses. A recent publication concluded that the most serious H-DI's are confined mainly to certain categories of drugs, namely the cardiovascular and central nervous systems, and involve mainly the same herbal products [1].

Mechanisms of drug interactions

Drug interactions arise by *pharmacokinetic* processes, which involve absorption, distribution, metabolism and excretion; and *pharmacodynamic* effects, which occur when the effects of one drug are altered by the presence of another at the site of action (true 'pharmacological' interactions). At present, much more is known about pharmacokinetic processes regarding herb-drug interactions.

The metabolism of any drug involves two parts. *Phase I* is catabolic and includes oxidation, reduction and hydrolysis, and which may also produce metabolites more active (or toxic) than the parent drug, for example aristolochic acid [5]. This phase is carried out mainly by cytochrome P450 isoenzymes which are present in the liver: these may be induced or inhibited. Other enzymes such as alcohol dehydrogenase, xanthine oxidase and monoamine oxidase may also be involved, and simple hydrolysis in plasma may occur. *Phase II* is anabolic, often to increase hydrophilicity and thus aid excretion; this may include glucuronide, acetyl, methyl and glutathione conjugation. The most significant H-DI's are caused by a change in the metabolism of either herb or drug, which can happen if they use the same enzyme pathway. If cytochrome P450 enzymes are induced, they will also metabolize faster any other drug *using the same pathway* , and this applies to the way in which St John's wort may *reduce* blood levels (and therefore efficacy) of the oral contraceptive pill, warfarin or digoxin. Conversely, enzyme inhibition leads to *increased* drug levels [5-10]. The other major mediator of H-DIs is P-glycoprotein, a 'pump' found in cell membranes (gut, blood-brain barrier etc), which affects serum drug levels by blocking or facilitating entry into cells. It can even eject drugs which have already been absorbed from the gut lining [10].

Problems specific to herbal products

Complexity and variability

HMPs are by definition complex mixtures of many compounds, leading to the possibility of a total extract having a different profile of H-DIs than an isolated compound. For example, genistein inhibits various CYP enzymes but the whole extract of soya, in which genistein occurs, does not [8]. Opposing effects have even been reported on the extracts of the same plant using *in vitro* and *in vivo* methods: in a study looking at the effect of a liquorice extract on CYP 3A4 using a microtitre plate assay of enzyme activity, *inhibition* was found [7], whereas the extract was reported to *increase* activity of the CYP3A family, and also of CYP1A2 and CYP2B1, after repeated dosing in rodents [8]. It is not known whether this is due to the extracts having a different composition, or whether it is a species specific effect, or perhaps it is an example of the difference between *in vitro* and *in vivo* results. This phenomenon illustrates once again the danger of extrapolating the results of *in vitro* or *in vivo* experiments, which examine the experimental effect of a single compound, on a possibly species specific enzyme, in a laboratory, to clinical situations. It is therefore most important that the association between experimental results and clinical situations is clarified to enable accurate predictions to be made, and that the contribution of a single ingredient in a mixture is put in perspective [11]. The constitution of a HMP can also vary greatly, depending on the source material, which is determined by genetics, and the conditions under which it is grown, as well as the method of processing, including extraction, storage, and formulation of the product [12].

Quality

The lack of proper regulation and licensing has led to a situation where it is difficult to guarantee the quality of some HMP's on sale. In many cases there is also an absence of data regarding their composition and mode of action [1]. Some herbs require specialist treatment after collection, for example the most highly esteemed quality of Asian ginseng comes from plants of certain varieties that are at least 7 years old, and which have been fermented and dried before processing. This makes them expensive and thus very liable to adulteration, the most common adulterant being liquorice, which has known adverse reactions, including an interaction profile different to that of ginseng. Mistaken identity and adulteration may account for inaccurate reports as to the safety of a herbal medicine and damages the reputation of a herb. Even more dangerous is the practice of adulteration of HMP's with synthetic medicines, such as corticosteroids and even warfarin [1].

Quality control and good manufacturing practice is therefore obviously of equal importance to herbal medicines as to conventional drugs, and when quality control methods can be further refined, H-DI reports will become more reliable. At present it is difficult to decide whether there is a true interaction or not, since the composition (and even the identity) of a herb within a HMP cannot always be validated. Even though reputable herbal manufacturers have quality assurance procedures in place, which minimise variability within their own products, there will inevitably be differences between preparations made by different methods and by different companies [12].

Methods

Retrieval of herb-drug interaction reports

The following strategy was used initially to survey the literature and access reports of the effects of herbal medicines on Cytochrome (Cyp) P450 enzymes and P-glycoprotein (P-gp); the computer databases Embase and Medline were accessed from their inception up to July 2006, using the key phrases 'herb-drug interaction', 'herbal medicine toxicity' and 'herbal pharmacokinetics'. Reviews identified by the computer searches [1-7] were consulted, to try and try and rectify any omissions by the abstracting services.

Results

The most important H-DIs are listed in table 1, together with some experimental results and their effects on Cyp enzymes and P-gp. All primary references, apart from those specifically cited in the table, which were published after 2005 [13-15], can be accessed from the review reference [1] but are not listed here for reasons of space.

Table 1: Reports of experimental and clinical herb-drug interaction potentials

Herb	Drug interaction potential
Agnus Castus (Chaste tree) *Vitex agnus castus*.	Theoretical possibility of interaction with dopaminergic drugs or hormone therapy
Ashwagandha *Withania somnifera*	Potentiates sedative effects of barbiturates and some benzodiazepines; avoid as a precaution
Berberis (Barberry) *Berberis vulgaris* and other spp	Berberine inhibits CYP2D6 and CYP3A4 *in vitro*.
Cat's claw (Uña de gato) *Uncaria tomentosa, U. guianensis*.	Extracts inhibit CYP3A4 and 2C9, so caution with substrates of CYP3A4 (eg cancer chemotherapy) and warfarin.
Chamomile (German or Hungarian) *Matricaria recutita*	Intreraction with warfarin reported in an elderly patient [13]; extract of *Matricaria* showed weak inhibition of CYP3A5 *in vitro*
Cinchona bark (Jesuit's bark) *Cinchona* species	Quinine alkaloid inhibits CYP2D6 but low levels have no effect
Cranberry *Vaccinium macrocarpon, V. oxycoccus*	Cases of interaction with warfarin reported; avoid concurrent use
Dan Shen *Salvia miltiorrhiza*	Mixture containing dan shen interacts with warfarin. Caution with digoxin. Extract inhibited CYPs 1A1/2, 2B1/2, 2E1 *in vitro* [14].
Dong quai (Dang gui, Chinese Angelica) *Angelica sinensis*	Possible interaction with warfarin in 1 case; pro-thrombin time lowered with concurrent administration in rabbits. Avoid with cancer chemotherapy

Echinacea (Coneflower). *Echinacea. purpurea*; *E. pallida*; *E. angustifolia*	*E. purpurea* selectively modulates CYP3A enzymes *in vitro*, reduces oral clearance of substrates of CYP1A2 (not CYP2C9 or CYP2D6). Caution with substrates of CYP3A4. *Echinacea* species differ chemically - results may not be applicable to all.
Evening primrose *Oenothera biennis*	Oil moderately inhibits in vitro activity of CYP3A4, CYP1A2, CYP2C9, CYP2D6 and CYP2C19. Possible clinical interaction with phenothiazines.
Garlic *Allium sativum*	Reduction of CYP2E1 activity in humans and some *animal* species; no increase in CYP2B1/2 in humans. Mild inhibition of P-gp *in vitro*. Single reports of increased bleeding time with lisinopril, warfarin. Reduces bioavailability of the protease inhibitor saquinavir and to a lesser extent ritonavir. Appears safe with most drugs except saquinavir.
Ginkgo *Ginkgo biloba*	Most reports unconfirmed. No effect on CYP1A2, CYP3A4, CYP 2E1 CYP2D6 activity in humans, but moderate inducer of CYP2C19. Interaction reported with omeprazole in Chinese patients and fatal seizures in a patient on antieplilepsy medication [15]. Caution if taken with warfarin, antiplatelet drugs, alprazolam, donezepil, trazodone, anticancer drugs.
Ginseng (Korean, Red) *Panax ginseng* **American ginseng** *Panax quinquefolius* **Siberian ginseng** *Eleutherococcus senticosus*	Suspected potentiation of phenelzine and nifedipine (a CYP3A4 substrate) in animal study. Enzyme-selective effects on other CYP's depend on nature of extract. Ginsenosides inhibit P-gp at high concentrations. Avoid with MAOI's, nifedipine, and in cancer chemotherapy. *P. quinquefolius* reduced effects of warfarin in healthy volunteers, but *P. ginseng* had no effect.
Goldenseal *Hydrastis Canadensis*	Extracts of inhibit CYP3A4 and displace protein binding to bilirubin *in vitro*. Berberine and hydrastine inhibit CYP2D6 and CYP3A4 *in vitro*.
Green tea *Camellia sinensis*	None reported. Catechins inhibit some CYP enzymes and P-gp, but inhibition of CYP enzymes thought to be reason for chemoprotectant effect of tea. Caution with warfarin. Caffeine induces CYP1A2.
Guarana *Paullinia cupana*	Caffeine (= guaranine) induces CYP1A2. Avoid with other stimulants
Kava-kava (Kava) *Piper methysticum*	Potent inhibitor of CYP3A4, CYP1A2, CYP2C9, CYP2D6, CYP2C19. Avoid with anticancer drugs and other sedatives
Liquorice (Licorice) *Glycyrrhiza glabra, G. uralensis* and others.	Increases activity of some CYP enzymes in rodents after repeated dosing BUT extract shows weak inhibition of CYP3A5 *in vitro*.
Ma Huang *Ephedra sinica*, other *Ephedra* spp.	Potential, theoretical interaction with MAOI's a serious possibility. Avoid use with MAOI's, other stimulants, halothane anaesthetics, anti-arrhythmics and all drugs contra-indicated with ephedrine
Milk thistle (St Mary's thistle) *Silybum marianum*.	Weak inhibition of P-gp-mediated cellular efflux; little effect on CYP enzymes including CYP3A4. No interference with pharmacokinetics of indinavir in healthy human subjects
Oregon grape (Mountain grape) *Berberis aquifolium (Mahonia aquifolium)*	Berberine and hydrastine inhibit CYP2D6 and CYP3A4 *in vitro*.
Peppermint *Mentha x piperita*	Inhibition of P-gp by extract and possibly oil.
Red clover *Trifolium pratense*	Red clover extract inhibits CYP3A4, and genistein inhibits several CYP enzymes *in vitro* and interacts with P-gp and other transporters. Theoretical considerations suggest avoidance with HRT, also tamoxifen and other treatments for breast cancer.
Rosemary *Rosmarinus officinalis*	None known. *In vitro* inhibition of P-gp

St John's wort *Hypericum perforatum*	High potential for interaction. Significant induction of CYP's 2E1, 3A4, 1A2, 2D6, 2C19. Competing effects on P-gp: initially inhibited then induced. Conflicting reports on theophylline: interaction reported, but SJW did not affect serum levels of theophylline (via CYP1A2) in human volunteers. Avoid with anticoagulants, oral contraceptives, immune suppressants, digoxin, opiates, antineoplastics, protease inhibitors, fexofenadine, statins, omeprazole, verapamil and other antidepressants
Soya *Glycine max*	No clinical reports, and conflicting evidence between effects of genistein, an isolated ingredient, and the total extract of soya. Genistein inhibits various CYP enzymes and P-gp, but soya extract does NOT affect CYP3A4. Theoretical considerations suggest avoidance with HRT, also tamoxifen and other treatments for breast cancer
Turmeric *Curcuma longa*	None known. Curcumin inhibits P-gp, but has very poor oral bioavailability. Caution in patients taking high doses with anticoagulants or antiplatelet drugs
Valerian *Valeriana officinalis*	Extract weakly inhibits CYP3A4, CYP2D6 and CYP2C19, may potentiate effects of barbiturates and chlorpromazine. Multiple night-time doses had minimal effect on CYP3A4 and no effect on CYP2D6 activity in human volunteers.

Conclusions

Most reported interactions involve prescription drugs are already well-documented for their potential to interact with many other medicines. They are most likely to be metabolised by the cytochrome P450 enzyme system, especially by CYP 3A4, and to a lesser extent CYP2C9, CYP2D6, CYP1A2 and others, as well as P-gp. Many are drugs with a narrow safety index, poor bioavailability, and where blood levels must remain stable for therapeutic efficacy. Vulnerable patients, such as the very ill, the elderly and children, and those with a complicated drug regime, and patients taking warfarin, clozapine, lithium digoxin, phenytoin and carbamazepine, should be monitored and asked about consumption of herbal products if problems are suspected. The other main types of drugs involved in reported H-DI's are the protease inhibitors, for HIV infection, and immunosuppressants, used after organ transplants; all of which are notorious for their interaction profiles.

The most commonly reported herb in H-DIs is St John's wort. It has proven enzyme-inducing properties and should be avoided in patients taking oral contraceptives, anticoagulants, immune suppressants, anti-neoplastics, protease inhibitors, digoxin, fexofenadine, statins, omeprazole, verapamil and other antidepressants. Other groups of patients at risk of interactions are transplant patients on immunosuppressive drugs, who should avoid HMPs - the consequences of H-DIs are too serious to risk. Similarly, patients on cancer chemotherapy should avoid concurrent use of HMP's as blood levels should be kept as predictable as possible. In summary, it appears that occasional use of HMP's, with the exceptions mentioned earlier, is unlikely to pose problems since at present most H-DI's appear to be the result of cytochrome P450 enzyme induction; however long-term use may increase their incidence. Although data is accumulating regarding the effects of herbs on CYP enzymes and P-gp, it must be remembered that a single *in vitro* or even *in vivo* experiment cannot be extrapolated to a clinical situation.

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