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Review

In vivo assessment of herb–drug interactions: Possible utility of a pharmacogenetic approach?

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Herbal medicines are frequently used in combination with conventional drugs and interactions are likely to be more common than those which manifest clinically. Pharmacokinetic interactions mediated by drug-metabolizing enzymes or transporters are involved in many herb–drug interactions. Polymorphisms in the genes for these enzymes and transporters may influence the interactions mediated through these pathways. Herb–drug interactions can be identified *in vivo* using the herbs with individual probe drugs or drugs with a narrow therapeutic index. A probe drug cocktail approach offers a more efficient screening procedure. If potential interactions are studied in subject groups with different genotypes, more definitive information can be obtained. The selection of genotype groups to study should depend not only on the major enzymes or transporters involved in the disposition of a drug, but also on alternate pathways which may become more important in subjects with reduced activity in the primary pathway, and the pathways for pharmacodynamic effects should also be considered for some drugs. Some genotypes may only be found in certain ethnic groups. Currently, the pharmacogenetic approach has been used mainly to study drug–drug interactions so there is considerable potential to extend this to the study of herb–drug interactions *in vivo*.

Keywords: Cytochrome P450 enzymes / Drug transporters / Ethnic differences / Herb–drug interactions / Pharmacogenetic

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1 Introduction

Herbal medicines are being used with increasing frequency on a worldwide basis and they are often used concomitantly with conventional medications so there is considerable potential for herb–drug interactions [1], particularly in patients with cancer and HIV/AIDS [2, 3]. Interactions between herbs and drugs can be identified in a variety of ways. Case reports and spontaneous reporting provide important sources of information and a number of these have been reviewed recently [4–6]. However, these may only identify the most extreme examples. In some countries, such as the United Kingdom, pharmacovigilance programs have been initiated to help identify adverse effects of herbal medicines [7]. Also the registration scheme for traditional herbal medicines in Europe has been simplified and the requirements to demonstrate efficacy made less stringent, but the license holders for these products are required to conduct postmarketing surveillance for their products and to report suspected adverse reactions [8]. However, the reporting rate of adverse reactions to herbs or conventional medicines is usually thought to be very low and the quality of the reports may be highly variable [9].

A more systematic approach for identifying herb–drug interactions is clearly desirable. This may be relatively easy to do in the *in vitro* situation as shown for example with flavonoids, for which there are a large number of the studies on the effects on some cytochrome P450 (CYP) enzymes and phase II enzymes, which were recently reviewed [10]. However, it is not always appropriate to extrapolate such *in vitro* studies to the *in vivo* situation, partly because many herb-derived compounds such as flavonoids have low oral bioavailability and may undergo metabolism themselves into products with different activities. Various methodolo-

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Abbreviations: ABC, adenosine triphosphate-binding cassette; **AUC,** area under the plasma concentration–time curve; **CYP,** cytochrome P450; **EM,** extensive metabolizer; **OATP,** organic anion transporting polypeptide; **P-gp,** P-glycoprotein; **PM,** poor metabolizer; **PXR,** pregnane X receptor; **SNP,** single nucleotide polymorphism

gies are available for conducting *in vitro* and *in vivo* studies to identify potential metabolic drug–drug interactions [11–13]. Drug interactions with other drugs or with herbs or dietary supplements which are mediated by drug-metabolizing enzymes may be identified most efficiently with a probe drug cocktail approach [14–16], but there is likely to be considerable variation in the degree of interaction between individuals *in vivo* for a variety of reasons including age [17], gender, underlying diseases such as liver cirrhosis [18], and pharmacogenetic factors [19].

Drug transporters are increasingly being recognized as having an important role in drug disposition and drug interactions [20–22] and as with the drug-metabolizing enzymes many polymorphisms have been identified in the genes for the transporters so there is considerable scope for pharmacogenetic factors to influence interactions mediated through these pathways. As with the drug-metabolizing enzymes, it is possible to study the interactions with transporters using *in vitro* systems such as the Caco-2 cell model of human intestinal transport, which shows functional expression of various human drug transporters. These studies can provide considerable insight into potential interactions but it is usually necessary to perform *in vivo* studies to confirm the *in vitro* findings. Furthermore, as the frequency of variant alleles often differs amongst ethnic groups, both for the drug-metabolizing enzymes and transporters (Tables 1 and 2), certain herb–drug interactions may be more easily identified in the ethnic group with the highest frequency of the relevant allele.

The recent study from Yin *et al*. [19] illustrates how herbs may react with drugs to a variable degree in subjects with different genotypes for the main metabolic pathway. Multiple doses of an extract of *Ginkgo biloba* reduced plasma concentrations of omeprazole by increasing the oxidative metabolism of omeprazole through CYP2C19 but not CYP3A4 and the effect was genotype-dependent being greater in the subjects with poor metabolizer (PM) genotype for CYP2C19. PMs of CYP2C19 are more common in East Asians and this interaction may never have been identified if it had only been studied in Caucasians.

Table 1. Allele frequencies of some common polymorphisms in drug-metabolizing enzymes in different ethnic groups [94–107]

Enzyme (polymorphism)	White (%)	Black (%)	East Asian (%)
CYP2C8[a]			
*2 (850A > T)	0–4.1	1.1–18	0[d]
*3 (416G > A; 1196A > G)	13	2	0[d]
*4 (792C > G)	0.2	14.1	0[d]
CYP2C9[a]			
*2 (430C > T)	10–15	2–4	0
*3 (1075 A > C)	5–10	<2	1–4
CYP2C19[a]			
*2 or m1 (681G > A)	13–19	11–25	21–45
*3 or m2 (636G > A)	0–0.3	0–1.8	5–13
CYP2D6[a]			
*3, *4, *5, *6, *etc.* (PMs)	20–25	6–7	6
*10(100C > T; 1661G > C, 4180G > C)	1.5–5	6	~50
*17(1023C > T; 1661G > C; 2850C > T; 4180G > C)	~0	30	~0
*2xN (*N* = 2,3,4,5, or 13)	5–10	1.9–13.6	0.5
CYP3A5[a]			
*1	0–15	36–45	23–40
*3 (6986A > G)	85–98	27–84	60–77
UGT1A1[b]			
*6 (211G > A)	0.7	NA[e]	5–24.1
*28 (−53(TA)$_{6>7}$)	29.5–40	34.6–44.6	6.8–23
*60(−3279T > G)	43.9–55	85	16.7–32.7
NAT2[c]			
M1 (digest with *Kpn*I)	45	30	0.7–5
M2 (digest with *Taq*1)	28	22	15.6–21
M3 (digest with *Bam*HI)	2	2	5.8–30.6
M4 (digest with *Msp*I/*Alu*I)	0	9	0

a) CYP, cytochrome P450.
b) UGT1A1, UDP-glucuronosyltransferase 1.
c) NAT2, *N*-acetyltransferase 2.
d) In 360 Japanese subjects.
e) NA, not available.

2 Polymorphisms in different ethnic groups

Genetic polymorphisms are important in determining interindividual and interethnic differences in drug disposition and response, and may also influence drug–drug and herb–drug interactions. There are more than 57 active human CYP genes and 58 pseudogenes known and the majority of the genes are polymorphic [23]. The most recent information on genetic variants of the CYP genes is available at the human CYP allele home page (http://www.imm.ki.se/CYPalleles/). Likewise, there is considerable genetic diversity in more than 600 transporter genes estimated in the human genome [24]. Most of the transporters belong to two major families of membrane transporters, the adenosine triphosphate-binding cassette (ABC) transporters and the solute carrier (SLC) transporters. Some of the common polymorphisms in clinically important drug-metabolizing enzymes and drug transporters which have a different distribution in different ethnic groups are shown in Tables 1 and 2.

CYP2C9 is important in the metabolism of many clinically important drugs, including warfarin and phenytoin, which both have a narrow therapeutic index. More than 100 single nucleotide polymorphisms (SNPs) have been described in the regulatory and coding regions of the CYP2C9 gene, and over 30 variant alleles have been reported to date [23]. CYP2C9*2 and CYP2C9*3 are the most common variant alleles in Caucasians (10–15 and 5–

Table 2. Allele frequencies of common SNPs or haplotypes of drug transporters in different ethnic groups [101, 104, 108–122]

	White (%)	Black (%)	East Asian (%)
SLCO1B1[a]			
*1a	NA[e]	NA[e]	35.2
*1b (388A > G)	30–46	75.0	64–87
*5 (521T > C)	14–20	2.3	11–16
*15 (388A > G; 521T > C)	2.7	NA[e]	7–10.3
ABCB1[b]			
3435C > T	48–54	16–26	37–47
2677G > T	41.6–46	0–3.6	6.5–10
2677G > A	0–0.5	36–43.7	5.8–21.8
1236C > T	34.4–42	15	61.5–69.4
−129T > C	5.9	NA[e]	1.6–8.3
ABCC2[c]			
1249G > A	15–21	14	~12
1446C > G	1.3–3.7	NA[e]	NA[e]
3563T > A	5	4	NA[e]
4544 G > A	5	17	NA[e]
ABCG2[d]			
34G > A	2–10.3	4	15–36
421C > T	9.0–14	0	28–35
376C > T	0	NA[e]	0.4–1.9

a) SLCO1B1, solute carrier organic anion transporter family member 1B1.
b) ABCB1, ATP-binding cassette B, P-glycoprotein.
c) ABCC2, ATP-binding cassette C, MRP2.
d) ABCG2, ATP-binding cassette G2, BCRP.
e) NA, not available.

10%, respectively), but they are quite rare in African (2–4 and <2%) and East Asian (1–4% and undetected) subjects. CYP2C19 is responsible for the metabolism of proton pump inhibitors such as omeprazole and lansoprazole, and also partly for diazepam. Two variant alleles (*2 and *3) account for over 95% of cases of poor metabolism and these are much more common in East Asians than in Caucasians or African Americans. These two common alleles are usually associated with production of truncated proteins rather than total absence of activity.

CYP2D6 is one of the most polymorphic of all known human CYPs and more than 100 different variants have been described [23]. Those alleles resulting in inactive enzymes (*3, *4, *5, *6, *7, *8, and *16) account for 99% of PMs in Caucasians. These are uncommon in East Asians but there is a common variant CYP2D6*10 which results in reduced enzyme activity in Asian populations with a frequency of 50% or more, which is relatively rare in Caucasians (1.5–5%) and Africans (6%). Another variant allele *17 has a high frequency in Blacks, but is almost absent in Caucasians and Asians.

The multidrug-resistance (MDR) transporter P-glycoprotein (P-gp) or ABCB1 is highly polymorphic with a remarkable racial difference in the frequencies of some SNPs. Two synonymous SNPs (C1237T in exon 12 and C3435T in exon 26) and a nonsynonymous SNP (G2677T, Ala893Ser) in exon 21 were found to be in linkage disequilibrium, resulting in an SNP haplotype [25]. The frequencies of the haplotypes of ABCB1 also vary in different ethnic groups. These genetic polymorphisms with significant ethnic specificity in their distribution may result in different degrees of herb–drug interactions in different ethnic groups.

3 Mechanisms of pharmacogenetic effects on herb–drug interactions

Just as polymorphisms in drug-metabolizing enzymes and drug transporters may affect their activity for different substrates, it is likely that some inducers or inhibitors may have different effects on the different polymorphic forms, depending upon the mechanism of the effect. This has already been studied with a number of drug–drug interactions. For instance, the selective serotonin reuptake inhibitor (SSRI) fluvoxamine, even in very low doses, is known to be an inhibitor of a number of CYP enzymes including CYP1A2 and CYP2C19 [26]. By inhibiting CYP2C19, fluvoxamine increases the systemic exposure to a number of proton pump inhibitor drugs that are metabolized through this pathway including omeprazole, lansoprazole, and rabeprazole, but the inhibitory effect was mainly seen in subjects with the extensive metabolizer (EM) genotype (CYP2C19*1 homozygotes) and to a lesser extent in EM heterozygotes, but not in those subjects with the PM genotypes (CYP2C19*2 or *3 homozygotes) [27–29]. On the other hand, fluvoxamine showed a moderate inhibition of the metabolism of the thiazolidinedione rosiglitazone, which is predominantly a substrate for CYP2C8, but the effect was the same in subjects with the different CYP2C8 genotypes (CYP2C8*1/*1, CYP2C8*1/*3, and CYP2C8*3/*3) [30].

Drug–drug interactions involving enzyme induction may also be genotype-dependent. Rifampicin is a potent nonspecific inducer of hepatic CYP enzymes including CYP2C19. Zhou *et al*. [31] showed that the activity of CYP2C19 could be induced with rifampicin in EMs but not PMs using mephenytoin as a probe [31]. In a subsequent study it was shown that the induction of CYP2C19 by rifampicin was gene dose-dependent for homozygous EMs and heterozygous PMs and that homozygous PMs with the m1 mutation did show a small degree of induction of 4′-hydroxylase activity indicated by increased 4′-hydroxymephenytoin urinary excretion [32]. It was suggested that this increase in 4′-hydroxylase activity should be through a nonCYP2C19 hydroxylase as the m1 mutation was considered as functionally inactive. The same explanation may apply to the induction of CYP2C19 PMs by *G. biloba* [19].

Another mechanism for pharmacogenetic differences to influence herb–drug interactions is when a drug has more

than one major pathway for metabolism, so that reduction in the enzyme activity in one pathway due to a PM genotype may divert more of the drug to an alternate pathway which may then be more susceptible to interactions with other drugs or herbs. An example of this is diazepam, which is metabolized by both CYP2C19 and CYP3A. Subjects who are PMs for CYP2C19 have higher systemic exposure to diazepam than EM subjects and omeprazole reduces diazepam clearance to a greater extent in EM subjects through the effect on CYP2C19 [33, 34]. Kosuge *et al*. [35] examined whether the CYP3A4 inhibitor diltiazem would have different effects on the pharmacokinetics and pharmacodynamics of diazepam in subjects who were EMs or PMs for CYP2C19 [35]. They found that the area under the plasma concentration–time curve (AUC) for diazepam was increased by 1.4-fold in the CYP2C19 PMs compared to EMs and that concomitant administration of diltiazem increased the AUC for diazepam in both EMs and PMs by about 25%. Using psychomotor tests for pharmacodynamic effects, they were not able to detect any difference between the CYP2C19 genotypes or from the drug–drug interaction, but they only used a 2-mg dose of diazepam and it is conceivable that this drug interaction could result in adverse effects in patients receiving larger doses of diazepam and that it would then be more obvious in CYP2C19 PMs [35].

Pharmacogenetic differences may also influence herb–drug interactions in less direct ways. For instance, when the pharmacodynamic pathway is dependent on particular genotypes, the effect of small changes in pharmacokinetics resulting from a herb–drug interaction may be magnified in susceptible individuals. Polymorphisms in the $beta_1$-adrenergic receptor gene are important determinants of the antihypertensive response to metoprolol [36], which in turn is metabolized by polymorphic CYP2D6 [37] so there are a number of sites in the pharmacokinetic–pharmacodynamic pathway where pharmacogenetics could influence an herb–drug interaction with this drug. Another example is with warfarin, for which the herb–drug interactions are described in detail in another article in this issue. It has recently been shown that variants in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1) are a major determinant of the response to warfarin [38], and that the VKORC1 genotype is the dominant genetic influence responsible for the lower mean dose of warfarin needed for the effective anticoagulation in Hong Kong Chinese, relative to Europeans [39]. Subjects with the VKORC1 genotype associated with requirement for a lower dose of warfarin may be more susceptible to herb–drug interactions which alter warfarin pharmacokinetics or pharmacodynamics such as that with danshen (*Salvia miltiorrhiza*), which has been reported to interact with warfarin in a number of case reports from Hong Kong [40–42]. Previous studies also showed that the interactions between warfarin and tramadol or celecoxib resulting in exaggerated anticoatulation or even extensive bleeding might be related to polymorphisms in CYP2D6 [43] or CYP2C9 [44].

4 Grapefruit juice interactions and pharmacogenetics

Grapefruit juice, although not really an herb, provides an interesting example of how a natural substance can have a major influence on drug deposition. Since the chance discovery of the interaction of grapefruit juice with felodipine some 15 years ago [45], extensive investigations have shown that the effect was related to selective downregulation of CYP3A4 in the small intestine [46, 47] and that it was mediated through constituents common to grapefruit juice and Seville orange juice, the furocoumarins bergamottin and 6′,7′-dihydroxybergamottin [48]. Grapefruit juice produces a mechanism-based irreversible inactivation of intestinal CYP3A4 resulting in reduced presystemic metabolism and increased oral bioavailability of drugs which show a high degree of metabolism through this pathway such as felodipine [49]. The effect seems to be confined to intestinal CYP3A4, presumably because the inhibitors are poorly absorbed, but it was suggested that very large doses of grapefruit juice might also inhibit hepatic CYP3A4 [50].

CYP3A4 exhibits a wide range of activity between individuals of 20-fold or more in human liver microsomes [51] and although it was suggested that much of the variation was due to genetic factors [52] functional polymorphisms related to the CYP3A4 gene are quite uncommon and their influence on grapefruit juice–drug interactions has not been studied to our knowledge. The most common variant CYP3A4*1B, with an adenine (A) to guanine (G) transition in the 5′ promoter region of the CYP3A4 gene at position –292, has an allele frequency ranging from 0% in East Asians to 55% in African Americans but it does not appear to alter substrate metabolism [53, 54]. In contrast, CYP3A5 does have some common functional variants which vary in frequency among different ethnic groups (Table 1) [55]. CYP3A5 is only expressed in a minority of individuals and the reference sequence, designated as *1 is not the most common allele, but it does encode for the protein with the highest activity [56]. CYP3A5*3 is the most common allele in most populations and is associated with the absence of hepatic CYP3A5 in homozygotes. In the study of the mechanism of grapefruit juice interaction with felodipine, colonic CYP3A5 was not inhibited [46], but CYP3A5 was not thought to be present in the small intestine in those subjects. However, the expression of CYP3A5 in the small intestine may be genotype-dependent as it is in the liver [57, 58] and as it will contribute to the overall activity of CYP3A enzymes it is possible that grapefruit juice may have different effects in subjects with different CYP3A5 genotypes, but again this does not appear to have been studied.

The interactions of grapefruit juice with CYP3A4 substrates may result in clinically relevant effects. For instance with the 1,4-dihydropyridines felodipine, nicardipine, nifedipine, nisoldipine, or nitrendipine, concomitant grapefruit juice may result in excessive vasodilatation with symptoms of flushing, tachycardia or symptomatic hypotension. Interactions with grapefruit juice have been shown for the HMG-CoA reductase inhibitors atorvastatin [59], lovastatin [60], and simvastatin [61] and taking grapefruit juice with a high dose of these drugs may increase the risk of rhabdomyolysis, although there do not appear to have been any published case reports of this adverse interaction. With other drugs with a relatively narrow therapeutic index such as cyclosporine [62, 63] or terfenadine [64], the interaction with grapefruit juice may be even more serious and potentially fatal [65]. Whether these interactions may differ in subjects with different CYP3A5 genotypes or in the rare subjects with functional CYP3A4 polymorphisms remains to be examined.

Studies would also be appropriate to examine the interactions with grapefruit juice using a pharmacogenetic approach in other enzyme pathways. Grapefruit juice increased the bioavailability of diazepam 3.2-fold by the inhibition of intestinal CYP3A4 [66] and this interaction might be predicted to result in very high AUC values for diazepam in PMs of CYP2C19 but this pharmacogenetic effect does not appear to have been studied. Like diazepam, lansoprazole undergoes metabolism through two pathways, the main one being 5-hydroxylation catalyzed by CYP2C19 and the other being sulfoxidation to lansoprazole sulfone catalyzed by CYP3A4/5 [67]. Compared with subjects with CYP2C19 EM genotype, PM subjects had higher total lansoprazole plasma concentrations and EM/PM heterozygotes had intermediate values [68]. Lansoprazole is also subject to enantioselective metabolism and plasma concentrations of (*R*)-lansoprazole are higher than those of the (*S*)-enantiomer, which appears to be because the (*S*)-enantiomer is cleared more rapidly by CYP2C19. In one study there was no effect of grapefruit juice on the pharmacokinetic parameters for each lansoprazole enantiomer or lansoprazole sulfone in all three CYP2C19 genotype groups suggesting the CYP3A4-mediated first-pass sulfoxidation of (*R*)- and (*S*)-lansoprazole were not influenced by grapefruit juice [69]. However, in another study grapefruit juice did result in a small but significant increase in the AUC of total lansoprazole in CYP2C19 PMs and a decrease in sulfoxidation index which was only significant in the CYP2C19 EMs [68]. This may suggest that grapefruit juice partially inhibits the formation of lansoprazole sulfone catalyzed by CYP3A4, which is consistent with the previous findings in an interaction study with omeprazole and grapefruit juice [70]. The findings with grapefruit and lansoprazole suggest there is a slight variation in the interaction with different CYP2C19 genotypes.

It has been controversial whether grapefruit juice might also enhance oral drug bioavailability through inhibition of P-gp reducing intestinal efflux transport [71]. A different constituent specific to grapefruit juice might be responsible for this effect as grapefruit juice, but not Seville orange juice caused an increase in the bioavailability of cyclosporine [48]. However, grapefruit juice had little effect on the pharmacokinetics of digoxin, which is considered to be a P-gp substrate with negligible metabolism [72], but this could be because P-gp does not contribute extensively to the oral bioavailability of digoxin [71].

When the interaction of grapefruit juice was tested with fexofenadine, another P-gp substrate, there was a surprisingly marked decrease in the AUC and peak plasma concentration (C_{max}) with no change in t_{max} or $t_{1/2}$ suggesting reduced bioavailability rather than increased systemic elimination [73]. This effect was attributed to inhibition of intestinal uptake transport organic anion transporting polypeptides (OATPs) and was also seen with orange juice and apple juice [73, 74]. Grapefruit juice produced a similar decrease in the bioavailability of talinolol, which is also a P-gp substrate, and it was speculated this might also be through inhibition of OATPs or other uptake transporters [75]. Genotype-dependent drug interactions with grapefruit juice are also possible as there are common polymorphisms in the genes for P-gp (*ABCB1*) and OATP (solute carrier organic anion transporter family member 1B1, *SLCO1B1*). These polymorphisms have different frequencies in different populations which could result in ethnic differences in the incidence of interactions (Table 2).

Many of the calcium channel blockers undergo stereoselective metabolism [76] and the inhibitory effect of grapefruit juice on the metabolism of a number of these drugs has been shown to be stereoselective with greater effects on the enantiomer which undergoes the greater presystemic metabolism [1, 77]. However, studies with amlodipine have been variable with one study showing no effect of grapefruit juice on either enantiomer of amlodipine [78] whereas an earlier study had shown small increases in C_{max} and AUC of total amlodipine when it was taken with grapefruit juice [79]. It was suggested that the differences in this effect between individuals could be related to genetic factors [80], but amlodipine undergoes very little presystemic metabolism with an absolute bioavailability of > 80% so the potential for inhibition of the metabolism by CYP3A4 in the intestine is limited, but polymorphisms of CYP3A4 or CYP3A5 could be involved.

5 St. John's wort interactions and pharmacogenetics

St. John's wort has been shown to reduce the plasma concentrations of many drugs by inducing the intestinal P-gp gene (*ABCB1*) and increasing intestinal and hepatic CYP3A4 activity [81 – 83] through activation of the pregnane X receptor (PXR) [84]. Drugs involved include ami-

triptyline, cyclosporine, digoxin, indinavir, irinotecan, warfarin, phenprocoumon, alprazolam, dextromethorphan, simvastatin, and oral contraceptives, although some studies did not find interactions with some of these drugs and certain preparations of St. John's wort [84]. Such pharmacokinetic effects may reduce the efficacy of the drug substrates of these enzymes or transporters and may even result in treatment failure. For example, treatment with St. John's wort for 4 weeks in hypercholesteroleamic patients on a stable dose of atorvastatin resulted in significant increases in total cholesterol and LDL cholesterol (from 2.34 mmol/L to 2.66 mmol/L, $p = 0.004$) levels consistent with increased metabolism of atorvastatin by induction of CYP3A4 [85]. Similar results were found with simvastatin and St. John's wort [86] and it is conceivable that such effects may vary in subjects with different polymorphic forms of CYP3A4 or CYP3A5 or of P-gp or the PXR.

The induction effect of St. John's wort on the activity of CYP3A4 or P-gp does not appear to have been examined directly in different genotypes but one study compared the inducibility of P-gp and CYP3A by St. John's wort among six ethnic groups using fexofenadine and midazolam as probes [87] and ethnic variations in the activity of P-gp and CYP3A do exist (Tables 1 and 2). The subjects were Caucasian, African American, Hispanic, Chinese, Indian, and Malay with five in each group and genotyping was performed for CYP3A4, CYP3A5, P-gp, and PXR. Coadministration of St. John's wort resulted in significant increases in the clearance of the P-gp substrate (fexofenadine) and the CYP3A substrate (midazolam) in all ethnic groups and there was no significant difference in the extent of induction of P-gp and CYP3A between the six ethnic groups. None of the individual genotype groups had a significant correlation with fexofenadine or midazolam pharmacokinetic parameters but lack of significance may be related to the small sample size and other factors contributing to inter-individual variability in this study and it would be useful to perform studies with larger groups with each genotype [87].

In addition to CYP3A4, some other P450 isoforms such as CYP2C9 are also induced by St. John's wort, but not CYP1A2 and CYP2D6 [88]. Wang *et al*. [89] investigated the effect of St. John's wort on CYP2C19 activity with respect to genotype. They found that St. John's wort treatment significantly increased CYP2C19 activity in the six EM (2C19*1/*1) subjects, with urinary 4-hydroxymephenytoin excretion raised by 151.5%, whereas no significant alteration was observed for CYP2C19 PM (four with 2C19*2/*2 and two with 2C19*2/*3) subjects, although the CYP2C19 activity overlapped somewhat between the EMs and PMs in the placebo phase. It would be predicted that as an inducer of CYP2C19, St. John's wort would have different effects on the systemic exposure to CYP2C19 drug substrates in patients with different CYP2C19 genotypes, but no study examining this directly appears to have been published yet.

6 Other herb–drug interactions and pharmacogenetics

Some important herb–drug interactions with clinical significance have been summarized elsewhere and many of these originate from case reports and limited clinical observations [4–6]. Some examples of herb–drug interactions mediated by CYP enzymes and drug transporters which might be subject to pharmocogenetic effects are listed in Table 3. In addition to St. John's wort, *Allium sativum* (garlic) could alter the pharmacokinetics of saquinavir by induction of CYP3A4 and P-gp. Similarly, *Silybum marianum* (milk thistle) could also interact with indinavir through modulation of CYP3A and P-gp. It was reported that *G. biloba* could increase the AUC of digoxin, which might be

Table 3. Herb–drug interactions which could have pharmocogenetic effects[a)]

Herb	Enzyme/transporter	Drug	References
Allium sativum (garlic)	Induction CYP3A4 and P-gp	Saquinavir, ritonavir	[123, 124]
Ginkgo biloba (ginkgo)	Modulation P-gp	Digoxin	[125]
	Induction CYP2C19	Omeprazole	[19]
Glycyrrhiza glabra (licorice)	Inhibition 11 b-hydroxysteroid dehydrogenase	Cortisol	[91, 92]
Hypericum perforatum	Induction CYP3A4 and P-gp	Amitriptyline	[126]
(St. John's wort)	Induction CYP3A4	Midazolam	[81, 127]
	Induction CYP2C19	Mephenytoin	[89]
	Induction CYP	Ciclosporin, imatinib, indinavir, tacrolimus, simvastatin	[128–135]
	Induction P-gp	Digoxin, fexofenadine	[136, 137]
Piper nigrum Linn (piperine)	Inhibition CYP	Propranolol, theophylline	[138]
Salvia miltiorrhiza (danshen)	Inhibition CYP2C9	Warfarin	[40, 139] [90]
Silybum marianum (milk thistle)	Modulation CYP3A P-gp	Indinavir	[140]

a) Adapted from Hu *et al*. [5].

mediated by modulation of P-gp. In healthy Chinese volunteers, *G. biloba* enhanced omeprazole hydroxylation in a CYP2C19 genotype-dependent manner [19] which suggested that caution should be used when patients take ginkgo and CYP2C19 substrates concomitantly, especially in PMs of CYP2C19.

S. miltiorrhiza (danshen) has also been found to enhance anticoagulation and increase the risk of bleeding when taken by patients on long-term warfarin therapy as mentioned above. In addition to the anticoagulant activity of danshen itself, a pharmacokinetic interaction with warfarin is also likely. Studies in rats showed danshen could increase the AUC and C_{max} of warfarin, which is mainly metabolized by CYP2C9 and to a lesser extent by CYP1A2 and CYP3A4 [90]. Piperine increased the AUC and C_{max} of propranolol and theophylline, both of which are metabolized by CYP2D6, CYP1A1, and CYP1A2 to a variable extent. The altered pharmacokinetics of these drugs appears to be caused by the inhibition of these CYP isoforms. Some polymorphisms in the genes for these enzymes will result in altered enzyme activity, which in turn may affect the herb – drug interactions in a genotype-dependent manner.

Glycyrrhiza glabra or *G. uralensis* (licorice) contain glycyrrhizin and glycyrrhetinic acid and are common ingredients in many herbal medicines, such as the traditional Chinese medicine gan cao. They alter steroid metabolism by inhibiting 11-β-hydroxysteroid dehydrogenase [91]. This reduces the deactivation of cortisol in the kidney, resulting in a mineralocorticoid effect with hypokalemia and sodium retention. These effects could interact with other drugs for instance by reducing the blood pressure lowering effect of some antihypertensive agents or increasing the sensitivity to digoxin. They also reduce the metabolism of some exogenous steroids such as prednisolone. [92] There is considerable scope for herb – drug interactions with this herb and there have been some case reports [93] but there do not seem to have been any systematic studies and no pharmacogenetic studies have been done.

7 Conclusions

The beneficial effects of herbal treatments are gradually being established in controlled clinical trials but there is still much to be done in identifying herb – drug interactions. Pharmacogenetic effects may play an important role in some herb – drug interaction and this has probably been underestimated. In many circumstances it is useful to employ an *in vivo* screening approach with single probe drugs or preferably the simultaneous use of a probe drug cocktail, which can provide real-time assessment of the enzyme activities of a range of CYPs and possibly other drug-metabolizing enzymes and transporters in an efficient and reliable manner. The addition of a pharmacogenetic approach can help to explore herb – drug interactions in greater depth and identify some interactions which may only occur in specific groups. This should ultimately lead to the most safe and effective use of drugs for individual patients.

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