PREDICTING PHARMACOKINETIC HERB-DRUG INTERACTIONS

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SUMMARY

In vitro and *in vivo* studies have indicated that the induction or inhibition of cytochrome P450 (CYP) is one of the major mechanisms for some clinically important pharmacokinetic herb-drug interactions. Thus, an attempt was made to predict pharmacokinetic herb-drug interactions using the pharmacokinetic principles that are used for predicting drug-drug interactions. The expected AUC ratio was mainly dependent on unbound herbal inhibitor concentration ([I]) and inhibition constant (K_i), hepatic fraction (f_h), number of inhibitory herbal constituents (n) and metabolic pathway fraction in hepatic metabolism (f_m). Herb-drug interactions would be with low risk if $\sum_{i=1}^{n} [[I_i]/K_{i(i)}]$ is less than 0.1, medium risk if it is between 0.1 and

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1.0, and high risk if it is greater than 1. For high clearance drugs, the change of $f_h \times f_m$ had minor influence on AUC ratio when $\sum_{i=1}^{n} [[I_i]/K_{i(i)}]$ values were fixed. Similarly, f_m did not affect the AUC ratio for low clearance drugs. It appeared likely to predict a herb-drug metabolic interaction when [I], K_i, f_h, f_m and n could be determined. However, many herb- and drug-related factors may cause difficulties with the prediction, and well-designed human studies are always necessary.

KEY WORDS

herb, metabolic inhibition, cytochrome P450, drug interactions

INTRODUCTION

Many commonly used herbs have been shown to modulate the plasma pharmacokinetics of important therapeutic drugs, leading to altered absorption, distribution, metabolism and excretion. For example, clinical studies have documented that St John's wort reduced the area of the plasma concentration-time curve (AUC) of cyclosporin /1,2/, amitriptyline /3/, digoxin /4/, indinavir /5/, nevirapine /6/, oral contraceptives /7/, warfarin /7/, phenprocoumon /8/, theophylline /9/, and simivastatin /10/. Garlic supplement decreased the plasma AUC and maximum plasma concentration (C_{max}) of the protease inhibitor saquinavir [11]; piperine increased C_{max} and AUC of phenytoin /11/, propranolol, and theophylline /12/. Moreover, glycyrrhizin from liquorice increased the plasma AUC of prednisolone /13/. Inhibition/induction of cytochrome P450 (CYP) has been suggested to be one of the major mechanisms for these reported herb-drug interactions /14/, although induction and/or inhibition of P-glycoprotein (PgP) may also play a role /15/.

Abbreviations: AUC = area of the plasma concentration-time curve; CL_{int} = intrinsic clearance; CYP = cytochrome P450; f_h = hepatic fraction; F_h = hepatic availability; f_m = metabolic pathway fraction in hepatic metabolism; [I] = unbound inhibitor concentration; K_i = inhibition constant; n = number of inhibitory herbal constituents; PgP = P-glycoprotein; R = the extent of inhibition of drug metabolism.

Herbs may inhibit CYPs by three mechanisms: competitive inhibition, non-competitive inhibition, and mechanism-based inhibition. Mutual competitive inhibition may occur between herbal constituent and drug, which are often metabolized by the same CYP enzyme. For example, diallyl sulfide from garlic is a competitive inhibitor of CYP2E1 /16/. Non-competitive inhibition is caused by the binding of herbal constituents containing electrophilic groups (e.g. imidazole or hydrazine group) to the heme portion of CYP. For example, piperine inhibited arylhydrocarbon hydroxylase (CYP1A) and 7-ethoxycoumarin deethylase (CYP2A) by a non-competitive mechanism /17/. Hyperforin present in St John's wort is a potent non-competitive inhibitor of CYP2D6 activity /18/. The mechanism-based inhibition of CYP is due to the formation of a complex between the herbal metabolite and CYP. Diallyl sulfone is a suicide inhibitor of CYP2E1 by forming a complex leading to autocatalytic destruction of CYP2E1 /19/.

To obtain successful predictions for herb-drug metabolic interactions, the following basic criteria should be met before quantitative correlations of *in vivo* pharmacokinetic data obtained from *in vitro* metabolic inhibition data based on *in vitro* models such as hepatic microsomes and hepatocytes /20-22/: a) drug clearance must be primarily through metabolism; b) drug is not subject to substantial conjugation or other non-CYP metabolism; c) the liver is the primary site of metabolic clearance; and d) the compound does not possess physiochemical properties that are associated with absorption problems (i.e. limited solubility, low intestinal permeability). The following factors determine the degree of change in the steady-state concentration (C_{ss}) and area of the plasma concentration-time curve (AUC) caused by the herb-drug interaction *in vivo*:

- The route of administration (intravenous or oral, i.e., whether the drug undergoes first-pass metabolism);
- Fraction (f_h) of hepatic clearance (CL_h) in total clearance (CL_{tot});
- Fraction (f_m) of the metabolic process subject to inhibition in CL_h;
- Unbound concentration of the inhibitory herbal component ([I]) around the CYP and inhibition constant (K_i);
- Plasma unbound concentration [S] of the drug subject to inhibition;
- Michaelis-Menten constant (K_m) for the drug subject to inhibition.

Unlike metabolic drug-drug interactions involving CYP inhibition for which a number of successful prediction cases have been reported /22/, the prediction of metabolic herb-drug interactions proves challenging and no reports on this have been published to our knowledge. An attempt was made to predict pharmacokinetic herb-drug interactions using the pharmacokinetic principles that are used for predicting drug-drug interactions.

PREDICTING PHARMACOKINETIC HERB-DRUG INTERACTIONS

The effects of inhibition of drug metabolism on *in vivo* pharmacokinetics are highly variable and depend on a number of factors associated with the drug and combined herb (dose and the route of administration) and patients. Generally, the extent of inhibition (R, %) of drug metabolism by herbal constituents depends on the inhibition mechanism when the substrate concentration [S] is high. For example, the R value of a particular metabolic pathway by a competitive inhibitor from co-administered herb can be calculated by Eq. 1 /23,24/:

$$R\,(\%) = \frac{[I]}{[I] + K_i \times (1 + [S]/K_m)} \times 100 \qquad \text{(Eq. 1)}$$

where [S] and [I] are the maximal unbound substrate and inhibitor concentration respectively; K_i, the inhibitory constant; and K_m, the Michaelis-Menten constant. When multiple inhibitory herbal constituents are involved, R is calculated by Eq. 2:

$$R\,(\%) = \sum_{i=1}^{n} \left[\frac{[I_i]}{[I_i] + K_{i(i)} \times (1 + [S]/K_m)} \times 100 \right] \qquad \text{(Eq. 2)}$$

In clinical situations, [S] is often much lower than K_m, then R is expressed by Eq. 3, independent of the inhibition nature, except for uncompetitive inhibition /25/:

$$R\,(\%) = \frac{1}{1 + K_i/[I]} \times 100 \qquad \text{(Eq. 3)}$$

From Eq. 3, given that both f_h and $f_m \rightarrow 1$, and f_u remains unchanged, it is clear that the AUC ratio (AUC′/AUC), the ratio of AUC in the presence of inhibitor over that in the absence of inhibitor, is calculated by Eq. 4:

$$\text{AUC ratio} = \frac{\text{AUC}'}{\text{AUC}} = \frac{\text{CL}_{int}}{\text{CL}_{int}'} = 1 + [\text{I}]/\text{K}_i \qquad \text{(Eq. 4)}$$

where CL_{int} is the intrinsic clearance inhibited by the inhibiting constituent; ' represents the value after alteration by herb-drug interaction. Since herbs usually contain multiple inhibitory constituents, a herb-drug interaction *in vivo* is considered likely if the following is true:

$$\text{AUC ratio} = 1 + \sum_{i=1}^{n} \left[[\text{I}_i]/\text{K}_{i(i)} \right] \qquad \text{(Eq. 5)}$$

where $[I_i]$ is the maximal unbound inhibitor concentration of each inhibitory constituent; $K_{i(i)}$, the inhibition constant for each constituent; n, the number of inhibitory constituents in the herb.

The expected AUC ratio in steady-state concentration or the AUC by an inhibiting constituent is dependent on the route of administration, as this will determine whether the drug undergoes first pass metabolism in the liver and/or the gut /22/. If drugs are administered by i.v. bolus, AUC ratio can be calculated by Eq. 6:

$$\text{AUC ratio} = \frac{\text{AUC}'}{\text{AUC}} = \frac{\text{C}_{ss}'}{\text{C}_{ss}} = \frac{\text{CL}_{tot}}{\text{CL}_{tot}'} = \frac{\text{CL}_h/\text{f}_h}{\text{CL}_h' + \text{CL}_h/\text{f}_h - \text{CL}_h}$$

$$= \frac{1}{\text{f}_h \times \text{CL}_h'/\text{CL}_h + 1 - \text{f}_h} \qquad \text{(Eq. 6)}$$

where f_h is the fraction of hepatic clearance in total clearance; CL_h is the hepatic clearance; and ' represents the value after alteration by drug interaction.

For high clearance drugs administered by i.v. bolus, CL_h is rate-limited by the flow rate. When the altered CL_h remains rate-limited by the flow rate, then $CL_h = CL_h'$, i.e. AUC ratio = 1, AUC is not altered. However, this is not true when the inhibition is extensive that CL_h is not limited by the flow rate. However, for a low clearance drug administered by i.v., the AUC ratio is given by Eq. 7.

$$\text{AUC ratio} = \frac{1}{f_h \times f_m \times CL_{int}'/CL_{int} + 1 - f_h \times f_m} \quad \text{(Eq. 7)}$$

where CL_{int} is the intrinsic clearance inhibited by the inhibiting constituent; ' represents the value after alteration by herb-drug interaction; and f_m is the fraction of the specific metabolic pathway in hepatic clearance. In clinical settings, [S] is often much lower than K_m, then the AUC ratio is given by the following equation:

$$\text{AUC ratio} = \frac{1}{f_h \times f_m \times \left\{\frac{1}{(1+[I]/K_i)}\right\} + 1 - f_h \times f_m} \quad \text{(Eq. 8)}$$

Obviously, the AUC ratio is determined by K_i, [I], f_h, and f_m, but not by K_m or [S]. It should be noted that multiple inhibitory herbal constituents are always involved in the inhibition of the same metabolic pathway of a drug, thus the AUC ratio is calculated by Eq. 9.

$$\text{AUC ratio} = \frac{1}{\sum_{i=1}^{n}\left[f_h \times f_m \times \left\{\frac{1}{(1+[I]/K_i)}\right\} + 1 - f_h \times f_m\right]} \quad \text{(Eq. 9)}$$

The change in AUC_{po} after a single oral administration and that in C_{ss} after repeated oral administration can be expressed by the following equation, if the dose and administration interval is constant:

$$\text{AUC ratio} = \frac{1}{[f_h \times CL_h'/CL_h + 1 - f_h] \times \frac{F_h}{F_h'}} \quad \text{(Eq. 10)}$$

where F_h is hepatic availability; ' represents the value after alteration by herb-drug interaction. Since the first-pass hepatic availability is close to unity for low clearance drugs, Eqs. 9 and 10 are also valid for low clearance drugs administered orally. However, for high clearance drugs administered by the oral route, the AUC ratio is given by Eq. 11, if the dose and administration interval is constant:

$$\text{AUC ratio} = \frac{1}{f_m \times \left\{\frac{1}{(1+[I]/K_i)}\right\} + 1 - f_m} \quad \text{(Eq. 11)}$$

When the herb contains multiple inhibitory constituents for CYP enzymes, the AUC ratio is calculated by Eq. 12.

$$\text{AUC ratio} = \frac{1}{\sum_{i=1}^{n}\left[f_m \times \left\{\frac{1}{(1+[I]/K_i)}\right\} + 1 - f_m\right]} \qquad \text{(Eq. 12)}$$

Obviously, it is necessary to know the values of K_i, [I], f_h, f_m, and n to predict *in vivo* metabolic herb-drug interactions. The values of f_h and f_m can be determined from the urinary recovery of the parent molecule and each metabolite. K_i can be estimated by *in vitro* inhibition studies using liver microsomes, hepatocytes and cDNA-expressed cytochromes. However, the determination of these parameters is difficult for herbs which often contain multiple components and low plasma levels are reached when administered.

RESULTS

The expected AUC ratio was mainly dependent on [I], K_i, f_h, number of inhibitory herbal constituents (n) and f_m. As shown in Figure 1 for Eq. 5, herb-drug interactions would be with low risk if $\sum_{i=1}^{n}\left[[I_i]/K_{i(i)}\right]$ is less than 0.1, medium risk if it is between 0.1-1.0, and high risk if it is greater than 1. Table 1 shows the estimated AUC

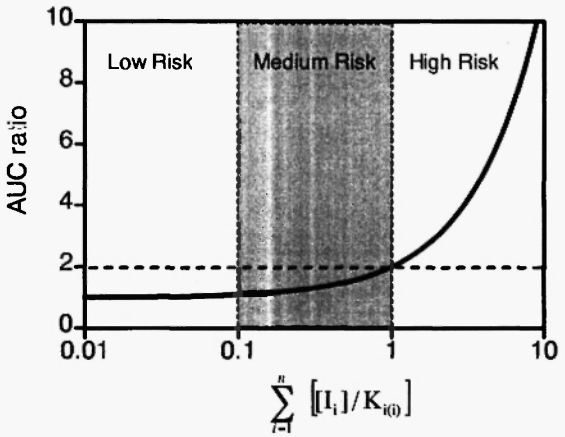

Fig. 1: Quantitative prediction of herb-drug interaction based on inhibitor concentration ($[I_i]$) and inhibition constant (K_i).

TABLE 1

$[I_i]$, K_i and AUC ratio for St John's wort, ginkgo and milk thistle

Herb	CYP inhibited	Major constituent	$[I_i]$ (μM)	K_i (μM)	$\sum_{i=1}^{n} [I_i]/K_{i(i)}$	Estimated AUC ratio (R)	Risk of herb-drug interaction
St John's wort	CYP1A2	I3,II8-Biapigenin	0.05	0.95	0.11	1.11	Medium
		Quercetin	0.2	3.3			
	CYP2C9	Hyperforin	1.0	1.8	0.66	1.66	Medium
		Hypericin	0.15	1.4			
	CYP2D6	Hyperforin	0.15	1.5	0.18	1.18	Medium
		I3,II8-Biapigemin	0.05	2.3			
		Hypericin	0.15	2.6			
	CYP3A4	Hyperforin	1.0	0.49	3.39	4.39	High
		I3,II8-Biapigenin	0.05	0.038			
		Hypericin	0.15	4.2			
Ginkgo	CYP1A2	Ginkgolide A	0.08	2.4	0.04	1.04	Low
		Ginkgolide B	0.01	2.4			

	CYP2C9	Ginkgolide A	0.08	0.9	0.09	1.09	Low
		Ginkgolide B	0.01	1.2			
	CYP2C19	Ginkgolide A	0.08	2.1	0.04	1.04	Low
		Ginkgolide B	0.01	2.2			
	CYP2D6	Ginkgolide A	0.08	3.9	0.02	1.02	Low
		Ginkgolide B	0.01	5.2			
	CYP3A4	Ginkgolide A	0.08	3.2	0.03	1.03	Low
		Ginkgolide B	0.01	3.4			
Milk thistle	CYP2E1	Silybin	2.1	28.7	0.08	1.08	Low
		Silydianin	0.2	65.8			
		Silycristin	0.1	36			
	CYP3A4	Silybin	2.1	4.9	0.47	1.47	Medium
		Silydianin	0.2	8.1			
		Silycristin	0.1	6.5			

AUC ratio was estimated using equation 5.

Data for St John's wort are from Obach *et al.* 2000 /18/; Biber *et al.* 1998 /33/ and Brockmoller *et al.* 1997 /34/. Data for Ginkgo are from Mauri *et al.* 2001/35/ and Zou *et al.* 2002 /36/. Data for milk thistle are from Weyhenmeyer *et al.* 1992 /37/ and Zuber *et al.* 2002 /38/.

ratio (based on Eq. 5) with regard to CYP isoform inhibited by individual herbal constituents using St John's wort, ginkgo and milk thistle as examples. It appears that St John's wort might cause medium to high risk for metabolic interactions with drugs that are primarily metabolized by CYP1A2, 2C9, 2D6 or 3A4, whereas both ginkgo and milk thistle would just cause low risk for metabolic interactions with drugs that are mainly eliminated by these enzymes, with an exception for CYP3A4 by milk thistle (AUC ratio = 1.47).

As shown in Table 2, the AUC ratio due to herb-drug combination can be estimated using Eq. 9. Coadministration of St John's wort was expected to significantly increase the AUC values of most CYP3A4 substrates such as carbamazepine, cyclosporine A, indinavir, midazolam and tacrolimus, but it would not remarkably change the AUC of caffeine, theophylline (both CYP1A2 substrates) and dextromethorphan (CYP2D6 substrate). Digoxin, a minimally metabolized drug by CYP3A4, would not interact with gingko due to metabolic interaction. However, these predictions did not fall into reasonable ranges except for theophylline (estimated vs observed AUC ratio: 1.07:1.00). Indeed, coadministered St John's wort significantly reduced AUC values of most combined CYP3A4 substrate drugs in humans /26/, indicating the induction of CYP3A4 and/or PgP. St John's wort caused no change of AUC for carbamazepine in humans. These findings reflect the difficulties and complexity when predicting herb-drug interactions.

The effects of coadministered herb depend on a number of factors associated with the herb, drug and the patient. For high clearance drugs (e.g. imipramine and propranolol), their CL_h is rate-limited by the hepatic blood flow rate (Q) but insensitive to changes in protein binding and enzyme activity. When $f_u \times CL_{int} >> Q$, $CL_h = Q$. Thus the change of $f_h \times f_m$ had minor influence on AUC ratio when $\sum_{i=1}^{n} [[I_i]/K_{i(i)}]$ values were fixed (Fig. 2). For low clearance drugs such as diazepam and tolbutamide, hepatic metabolism often constitutes the major pathway of their elimination, and CL_h of these drugs is mainly affected by changes in their binding to plasma proteins (but not affected by hepatic blood flow). Thus, the f_m values (usually >0.75) of these drugs did not significantly affect the AUC ratio.

TABLE 2

Predicted metabolic herb-drug interactions

Herb + Drug	$\sum_{i=1}^{n} [[I_i]/K_{i(i)}]$	Major CYP involved	f_h	f_m	Estimated AUC ratio	Observed AUC ratio	Ref.
St John's wort							
Caffeine	0.11	1A2	0.95	0.79	1.08	0.80	/39/
Carbamazepine	3.39	3A4	0.80	0.65	1.97	0.99	/40/
Cyclosporine A	3.39	3A4	0.94	0.76	2.63	0.54	/41/
Indinavir	3.39	3A4	0.85	0.70	2.20	0.43	/5/
Dextromethorphan	0.18	2D6	0.88	0.82	1.13	0.8	/39/
Midazolam	3.39	3A4	0.88	0.75	2.42	0.50-0.80	/42,43/
Tacrolimus	3.39	3A4	0.86	0.70	2.22	0.42-0.65	/44,45/
Theophylline	0.11	1A2	0.84	0.69	1.06	1.00	/46/
Ginkgo							
Digoxin	0.03	3A4	0.10	0.05	1.02	1.20	/40/
Milk thistle							
Indinavir	0.47	3A4	0.85	0.70	1.24	0.91	/47/

AUC ratio was estimated using equation 9.

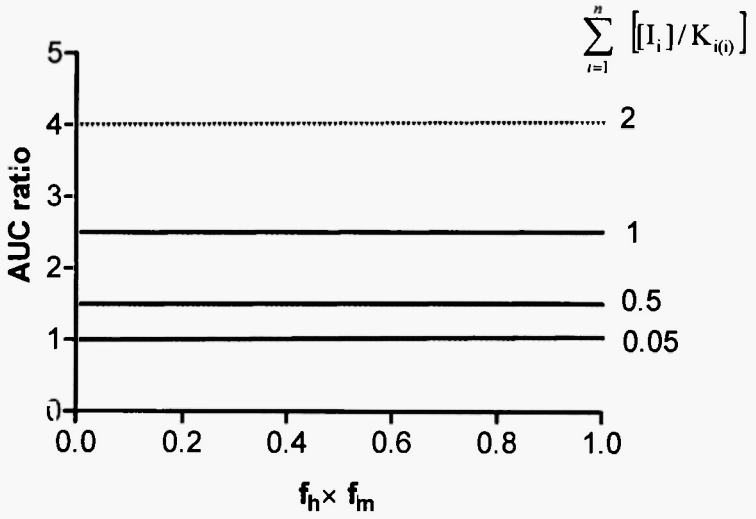

Fig. 2: Effect of hepatic (f_h) and metabolic (f_m) fraction on the AUC ratio.

DISCUSSION

A major safety concern is potential interactions of herbal products with prescribed drugs. This issue is especially important with respect to drugs with narrow therapeutic indexes (e.g. warfarin and digoxin) /27/. This may lead to adverse reactions that are sometimes life-threatening or lethal /28/. The clinical importance of herb-drug interactions depends on factors that are related to drug (dose, dosing regimen, and administration route) and patient (genetic polymorphism, age, gender, and pathological condition) /29/. Generally, a doubling or more in plasma drug concentration/AUC has the potential for enhanced adverse or beneficial drug response. However, less marked pharmacokinetic interactions may still be clinically important for drugs with a steep concentration-response relationship or narrow therapeutic index. In most cases, the extent of herb-drug interaction varies markedly among individuals, depending on inter-individual differences in drug metabolizing enzymes (in particular CYP3A4) and transporters (e.g. PgP), existing medical conditions, age, and other factors. This will make the prediction of herb-drug metabolic interactions difficult.

There is importance in the prediction of herb-drug metabolic interactions, as toxic or fatal herb-drug interactions may be avoided. The present study attempted to predict herb-drug interactions based on pharmacokinetic principles used for predicting drug-drug interactions. It appeared likely to predict an herb-drug metabolic interaction if [I], K_i, f_h, f_m and n could be determined. It is apparent that the determination of both [I] and K_i is the one of the most important but also the most difficult step for prediction of herb-drug interaction.

However, unlike the prediction of metabolic drug-drug interactions where there have been a number of successes with those drugs mainly metabolized by CYP enzymes /30/, the prediction of herb-drug metabolic interaction appears difficult for the following reasons: a) herb preparations may contain multiple CYP-modulating constituents, with unknown amounts and inhibition/induction potency for CYPs; b) the inhibition/induction of CYPs by herbs may by temporally distinguishable, depending on the dose of the herb, administration route and tissues; c) many herbs are used chronically; d) marked variability in the content of herbal constituents /31/; and e) drug-related factors such as inappropriate design of *in vitro* experiments; presence of extrahepatic metabolism; and active transport in liver. In addition, the *in vitro* scaling of kinetic and inhibition data from human tissues is more complex, particularly as the metabolism of many drugs by CYP3A4, which metabolizes >50% of therapeutic drugs, is inconsistent with classical Michaelis-Menten kinetic models /23,32/.

ACKNOWLEDGEMENTS

The authors gratefully appreciate the support by the National University of Singapore Academic Research Funds.

REFERENCES

1. Moschella C, Jaber BL. Interaction between cyclosporine and *Hypericum perforatum* (St. John's wort) after organ transplantation. Am J Kidney Dis 2001; 38: 1105-1107.
2. Breidenbach T, Kliem V, Burg M, Radermacher J, Hoffmann MW, Klempnauer J. Profound drop of cyclosporin A whole blood trough levels caused by St. John's wort (*Hypericum perforatum*). Transplantation 2000; 69: 2229-2230.

3. Johne A, Schmider J, Brockmoller J, Stadelmann AM, Stormer E, Bauer S, et al. Decreased plasma levels of amitriptyline and its metabolites on co-medication with an extract from St. John's Wort (*Hypericum perforatum*). J Clin Psychopharmacol 2002; 22: 46-54.
4. Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). Clin Pharmacol Ther 1999; 66: 338-345.
5. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. Lancet 2000; 355: 547-548.
6. de Maat MM, Hoetelmans RM, Mathot RA, van Gorp EC, Meenhorst PL, Mulder JW, et al. Drug interaction between St John's wort and nevirapine. AIDS 2001; 15: 420-421.
7. Yue QY, Bergquist C, Gerden B. Safety of St John's wort (*Hypericum perforatum*). Lancet 2000; 355: 548-549.
8. Maurer A, Johne A, Bauer S. Interaction of St. John's wort extract with phenprocoumon. Eur J Clin Pharmacol 1999; 55: A22.
9. Nebel A, Schneider BJ, Baker RK, Kroll DJ. Potential metabolic interaction between St. John's wort and theophylline. Ann Pharmacother 1999; 33: 502.
10. Sugimoto K, Ohmori M, Tsuruoka S, Nishiki K, Kawaguchi A, Harada K, et al. Different effects of St John's Wort on the pharmacokinetics of simvastatin and pravastatin. Clin Pharmacol Ther 2001; 70: 518-524.
11. Bano G, Amla V, Raina RK, Zutshi U, Chopra CL. The effect of piperine on pharmacokinetics of phenytoin in healthy volunteers. Planta Med 1987; 53: 568-569.
12. Bano G, Raina RK, Zutshi U, Bedi KL, Johri RK, Sharma SC. Effect of piperine on bioavailability and pharmacokinetics of propranolol and theophylline in healthy volunteers. Eur J Clin Pharmacol 1991; 41: 615-617.
13. Chen MF, Shimada F, Kato H, Yano S, Kanaoka M. Effect of oral administration of glycyrrhizin on the pharmacokinetics of prednisolone. Endocrinol Jpn 1991; 38: 167-174.
14. Zhou SF, Gao YH, Wen QJ, Huang M, Xu AL, Paxton JW. Interactions of herbs with cytochrome P450. Drug Metab Rev 2003; 35: 35-98.
15. Zhou SF, Lim LY, Chowbay B. Herbal modulation of P-glycoprotein. Drug Metab Rev 2004; 36: 57-104.
16. Teyssier C, Guenot L, Suschetet M, Siess MH. Metabolism of diallyl disulfide by human liver microsomal cytochromes P-450 and flavin-containing monooxygenases. Drug Metab Dispos 1999; 27: 835-841.
17. Dalvi RR, Dalvi PS. Comparison of the effects of piperine administered intragastrically and intraperitoneally on the liver and liver mixed-function oxidases in rats. Drug Metab Drug Interact 1991; 9: 23-30.
18. Obach RS. Inhibition of human cytochrome P450 enzymes by constituents of St. John's wort, an herbal preparation used in the treatment of depression. J Pharmacol Exp Ther 2000; 294: 88-95.
19. Jin JX, Baillie TA. Metabolism of the chemoprotective agent diallyl sulfide to glutathione conjugates in rats. Chem Res Toxicol 1997; 10: 318-327.

20. Ito K, Brown HS, Houston JB. Database analyses for the prediction of in vivo drug-drug interactions from in vitro data. Br J Clin Pharmacol 2004; 57: 473-486.
21. Ito K, Iwatsubo T, Kanamitsu S, Nukajima Y, Sugiyama Y. Quantitative prediction of in vivo drug clearance and drug interactions from in vitro data on metabolism, together with binding and transport. Annu Rev Pharmacol Toxicol 1998; 38: 461-499.
22. Ito K, Iwatsubo T, Kanamitsu S, Ueda K, Suzuki H, Sugiyama Y. Prediction of pharmacokinetic alterations caused by drug-drug interactions: metabolic interaction in the liver. Pharmacol Rev 1998; 50: 387-411.
23. Lin JH. Applications and limitations of interspecies scaling and in vitro extrapolation in pharmacokinetics. Drug Metab Dispos 1998; 26: 1202-1212.
24. von Moltke LL, Greenblatt DJ, Schmider J, Wright CE, Harmatz JS, Shader RI. In vitro approaches to predicting drug interactions in vivo. Biochem Pharmacol 1998; 55: 113-122.
25. Tucker GT. The rational selection of drug interaction studies: implications of recent advances in drug metabolism. Int J Clin Pharmacol Ther Toxicol 1992; 30: 550-553.
26. Zhou SF, Chan E, Pan SQ, Huang M, Lee EJD. Pharmacokinetic interactions of drugs with St John's wort. J Psychopharmacol 2004; 18: 269-283.
27. Heck AM, DeWitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. Am J Health-System Pharm 2000; 57: 1221-1227.
28. Elvin-Lewis M. Should we be concerned about herbal remedies? J Ethnopharmacol 2001; 75: 141-164.
29. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 2000; 38: 41-57.
30. Houston JB. Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance. Biochem Pharmacol 1994; 47: 1469-1479.
31. Bergonzi MC, Bilia AR, Gallori S, Guerrini D, Vincieri FF. Variability in the content of the constituents of *Hypericum perforatum* L. and some commercial extracts. Drug Dev Ind Pharm 2001; 27: 491-497.
32. Houston JB, Kenworthy KE. In vitro-in vivo scaling of CYP kinetic data not consistent with the classical Michaelis-Menten model. Drug Metab Dispos 2000; 28: 246-254.
33. Biber A, Fischer H, Romer A, Chatterjee SS. Oral bioavailability of hyperforin from hypericum extracts in rats and human volunteers. Pharmacopsychiatry 1998; 31: 36-43.
34. Brockmoller J, Reum T, Bauer S, Kerb R, Hubner WD, Roots I. Hypericin and pseudohypericin: pharmacokinetics and effects on photosensitivity in humans. Pharmacopsychiatry 1997; 30: 94-101.
35. Mauri P, Simonetti P, Gardana C, Minoggio M, Morazzoni P, Bombardelli E, et al. Liquid chromatography/atmospheric pressure chemical ionization mass spectrometry of terpene lactones in plasma of volunteers dosed with *Ginkgo biloba* L. extracts. Rapid Commun Mass Spectrometr 2001; 15: 929-934.

36. Zou L, Harkey MR, Henderson GL. Effects of herbal components on cDNA-expressed cytochrome P450 enzyme catalytic activity. Life Sci 2002; 71: 1579-1589.
37. Weyhenmeyer R, Mascher H, Birkmayer J. Study on dose-linearity of the pharmacokinetics of silibinin diastereomers using a new stereospecific assay. Int J Clin Pharmacol Ther Toxicol 1992; 30: 134-141.
38. Zuber R, Modriansky M, Dvorak Z, Rohovsky P, Ulrichova J, Simanek V, et al. Effect of silybin and its congeners on human liver microsomal cytochrome P450 activities. Phytother Res 2002; 16: 632-638.
39. Wenk M, Todesco L, Krahenbuhl S. Effect of St John's wort on the activities of CYP1A2, CYP3A4, CYP2D6, *N*-acetyltransferase 2, and xanthine oxidase in healthy males and females. Br J Clin Pharmacol 2004; 57: 495-499.
40. Burstein AH, Horton RL, Dunn T, Alfaro RM, Piscitelli SC, Theodore W. Lack of effect of St John's wort on carbamazepine pharmacokinetics in healthy volunteers. Clin Pharmacol Ther 2000; 68: 605-612.
41. Bauer S, Stormer E, Johne A, Kruger H, Budde K, Neumayer HH, et al. Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. Br J Clin Pharmacol 2003; 55: 203-211.
42. Wang ZQ, Gorski C, Hamman MA, Huang SM, Lesko LJ, Hall SD. The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. Clin Pharmacol Ther 2001; 70: 317-326.
43. Dresser GK, Schwarz Ul, Wilkinson GR, Kim RB. Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. Clin Pharmacol Ther 2003; 73: 41-50.
44. Mai I, Stormer E, Bauer S, Kruger H, Budde K, Roots I. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. Nephrol Dial Transplant 2003; 18: 819-822.
45. Hebert MF, Park JM, Chen YL, Akhtar S, Larson AM. Effects of St. John's wort (*Hypericum perforatum*) on tacrolimus pharmacokinetics in healthy volunteers. J Clin Pharmacol 2004; 44: 89-94.
46. Morimoto T, Kotegawa T, Tsutsumi K, Ohtani Y, Imai H, Nakano S. Effect of St. John's wort on the pharmacokinetics of theophylline in healthy volunteers. J Clin Pharmacol 2004; 44: 95-101.
47. Piscitelli SC, Formentini E, Burstein AH, Alfaro R, Jagannatha S, Falloon J. Effect of milk thistle on the pharmacokinetics of indinavir in healthy volunteers. Pharmacotherapy 2002; 22: 551-556.