Interactions Between Chinese Herbal Medicines and Drugs

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ABSTRACT

The popular use of herbal products in the general community raises concerns for potential herb–drug interactions. The risk of herb–drug interactions is increased if the herbal medicines are used concurrently with drugs which have a narrow therapeutic range, or are used in certain groups of patients, such as the elderly or those with impaired liver and renal functions. This short paper reviews some important concepts in herb–drug interactions and cases involving Chinese herbal medicines. It is important for Chinese medicine practitioners to understand, monitor and report potential herb–drug interactions.

KEYWORDS herb–drug interactions, Chinese herbal medicine, efficacy, safety, adverse reactions, cytochrome P450.

Introduction

Chinese herbal medicine, as one of the most developed remedies in traditional Chinese medicine, has been widely used by Chinese medicine practitioners for the treatment of a variety of acute and chronic diseases and conditions for thousands of years. Generally speaking, most Chinese herbal medicine practitioners are familiar with the concept of herb–herb interactions according to Chinese medicine theory, such as the synergistic/additive and/or antagonistic actions of some Chinese herbs under certain clinical conditions. However, many practitioners are less familiar with herb–drug interactions, possibly due to a limited understanding of the mechanisms underlying herb–drug interactions or difficulties in accessing existing data in this area.

The significant increase in the use of herbal medicines in the Australian community also raises concerns of potential toxicity of herbal products, including Chinese herbal medicines.[1] Such concerns are valid, considering some consumers or patients may take these products concomitantly with multiple conventional drugs for various conditions (particularly for chronic diseases and conditions in the elderly). The recent report to the Parliamentary Secretary to the Minister for Health and Ageing of Australia, prepared by the Expert Committee on Complementary Medicines, has identified potential herb–drug interactions as an important area, and encourages more research on the safety of herbal and other complementary therapies.[2]

In this short paper, we have outlined some important aspects of herb–drug interactions in the context of Chinese herbal medicines. It is important for Chinese herbal medicine practitioners to understand these concepts in order to optimise clinical therapies and to avoid potential adverse reactions related to Chinese herbal medicines.

What is a herb–drug interaction?

A herb–drug interaction is defined as any pharmacological modification caused by a herbal substance(s) to another exogenous chemical (e.g. a prescription medication) in the diagnostic, therapeutic, or other action of a drug in or on the body.[3] This relates to so called drug–drug interactions

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(interactions between drugs), herb–herb interactions (interactions between herbs) or drug–food interactions (interactions between drugs and food). Broadly speaking, the herb–drug interaction is also a kind of drug interaction, considering that the action of a herbal substance is eventually caused by chemical ingredients which may be known or unknown. For example, St John's Wort (*Hypericum perforatum*), a commonly used antidepressant herb, has been reported to cause significant changes in the action of cyclosporine A in transplant patients (for references, see Table 1). It also decreased plasma concentrations of a range of drugs including digoxin,[4] warfarin[5] and theophylline.[6] It should be pointed out that some herb–drug interactions may be beneficial, e.g. enhancing the efficacy or reducing the adverse reactions of an anti-cancer agent. Recently, a randomised clinical trial has demonstrated that Chinese herbal medicine reduces chemotherapy-induced nausea.[7] However, many herb–drug interactions can also be harmful, e.g. causing adverse reactions or therapeutic failure.

Why are we concerned about herb–drug interactions?

The main reason for concern is that herb–drug interactions may potentially affect the clinical safety and efficacy of related drugs or herbs. Although many interactions between herbs and drugs may be too minor (in terms of pharmacokinetic and/or pharmacodynamic changes) to have any clinical significance, in some cases, these interactions may alter the clinical outcomes or the safety of the treatment involved. The risk of harmful herb–drug interactions is of particular concern to both consumers and practitioners of herbal and conventional medicines. There has been an increasing number of reports on harmful herb–drug interactions globally, partly due to the popularity of using herbal products in the general population.[8]

It is important to note that the use of multiple medicines will significantly increase the risk of potential herb–drug interactions, especially in the elderly or certain groups of consumers, such as cancer patients. The risk for drug interactions increases with the number of products consumed. For example, the risk for potential interactions when consuming two products is 6%; five products, 50%; the risk increases to 100% when consuming eight or more products.[9] The likelihood of herb–drug interactions is therefore theoretically higher than drug–drug interactions since most synthetic drugs usually contain a single chemical entity.

It should be pointed out, however, that our understanding of the interactions between herbs and drugs is still limited. It is difficult to characterise and identify definitely a herb–drug interaction based only on case reports or case series studies. Considering a significant number of patients or herbal consumers fail to disclose the use of herbal products to their physicians,[10] and most physicians have relatively limited knowledge of various herbal products, the risk of potential herb–drug interactions is increased. Thus, there have been efforts for implementation of co-ordinated toxicity-monitoring systems by the World Health Organization (WHO) (e.g. WHO Collaborating Centre for International Drug Monitoring, www.who-umc.org), and by various governments, including those of Australia, the United Kingdom, the United States, Singapore and China, aimed at improving monitoring and timely reporting of potential herb–drug interactions.

How do herb–drug interactions occur?

Herb–drug interactions can be caused by various factors. They may result from chemical reactions between different ingredients, or from changes or modifications to specific biochemical pathways involved in the metabolism or actions of related drugs or herbs. For example, certain Chinese herbs may interfere with the body's drug transporters and metabolism enzymes, resulting in changes of the metabolism and consequently the actions of various drugs.

Most herb–drug interactions are mediated by pharmacodynamic and/or pharmacokinetic mechanisms. Pharmacodynamic interactions involve synergistic or antagonistic interactions on the same drug targets, e.g. receptors, which can often be predicted and avoided. For example, Ma Huang (*Ephedra* species) contains ephedrine-like alkaloids which exhibit sympathomimetic activities. Thus, Ma Huang may interact with other sympathomimetic agents, resulting in increased actions of monamine oxidase inhibitors and adrenergic agonists such as clonidine, and decreased actions of bethanidine and guanethidine.[11] Pharmacokinetic interactions are much more difficult to anticipate, as they occur through multiple mechanisms, including alterations of the drug's absorption, distribution, metabolism and excretion. Most reported herb–drug interactions are pharmacokinetic interactions. For example, certain herbal ingredients may inhibit P-glycoprotein-mediated drug transport in the liver and intestinal tract, resulting in changes of absorptions and actions of drugs which are P-glycoprotein substrates.[12,13]

Cytochrome P450 (CYP450) enzymes are the most important drug-metabolising enzymes in the body and are responsible for the metabolism of more than 50% of therapeutic drugs.[14] Herb–drug interactions often occur when CYP450 enzymes are affected. In humans, there are 57 CYP450 isoenzymes, and these are grouped into different classes or families. The nomenclature of CYP450s employs a three-tiered classification based on the conventions of molecular biology, indicated by

an Arabic numeral (family), a capital letter (subfamily) and another Arabic numeral (gene), e.g. CYP1A2.[15] Most drug oxidations are catalysed primarily by six CYP450 enzymes (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4/5). Among these, CYP3A4 is responsible for metabolising more than 50% of drugs which are CYP450 substrates.[14]

The actions of CYP450 may be changed by herbal ingredients through two different mechanisms: induction and inhibition. The induction of CYP450 usually requires a longer period of time (e.g. several days), which may lead to decreased drug plasma levels (through increased drug metabolism), and consequently reduced drug effects. Conversely, the inhibition of CYP450 is usually immediate and may lead to increased drug plasma levels (through decreased drug metabolism), and thus increased drug effects, which may result in significant adverse reactions or toxicities. Many clinical adverse events have been associated with CYP450 inhibitions.

In addition to P450s, there are also other drug metabolism enzymes and transport proteins which may be modulated by herbal substances, such as UDP-glucuronosyltransferase (UGT) enzymes and breast-cancer resistance proteins.

Examples of herb–drug interactions

A number of herb–drug interactions have been identified in humans,[12,16] as shown in Table 1. The reported drugs include warfarin, aspirin, phenprocoumon, midazolam, alprazolam, amitriptyline, oral contraceptives, indinavir, ritonavir, saquinavir, digoxin, cyclosporine, tacrolimus, imatinib and irinotecan.[12] There are also numerous studies on animals or cells indicating potential herb–drug interactions, although the relevance of the evidence to humans has yet to be established.

One of the most commonly reported drugs involved in herb–drug interactions is warfarin. More than 15 different herbs were reported to interfere with warfarin (and related drugs, such as heparin, aspirin, and coumarin derivatives). A number of Chinese herbs may potentially interact with warfarin, to cause bleeding. Such herbs include Ginger (*Zingiber officinale*), Ginseng (*Panax* species), Danshen (*Salvia miltiorrhiza*) and Dang gui (*Angelica sinensis*)[17,18] (Table 1).

One of the most commonly reported herbs involved is St John's Wort (*Hypericum perforatum*), which has been reported to interfere with cyclosporine, digoxin, theophylline, oral contraceptives, methadone, fluoxetine and buspirone (Table 1). For example, a number of cases have been reported showing that St John's Wort decreased cyclosporine blood concentrations.[19-27] *Gingko biloba* was also reported to interact with ibuprofen, trazodone, fluoxetine, buspirone and phenytoin (Table 1). It is interesting to note that both warfarin and cyclosporine are well-known subtracts of CYP2C9 and CYP3A4 respectively. St John's Wort is a potent inducer of CYP3A4 and P-glycoprotein.

Another example is Gancao (licorice, *Glycyrrhiza glabra*), which was reported to increase the plasma concentrations of prednisolone[28,29] by inhibiting the metabolism of prednisolone, and also potentiating the skin vasoconstrictive action of hydrocortisone.[30] Thus, it may potentially modify the pharmacological effects of prednisolone and hydrocortisone.

How to predict the risk of potential herb–drug interactions

Generally speaking, herb–drug interactions are difficult to predict as they depend on a number of factors, including the conditions of a patient, dose and time of administration of drugs and herbs, and quality of herbal substances. Often the individual differences may determine the consequences of a likely herb–drug interaction.

Given the chemical complexity of herbal compositions, it may be easier to predict the potential interactions based on the pharmacological properties of the drug or herb involved (e.g. if the drug or herb has similar or different pharmacodynamic actions, or acts as the substrate or inhibitor/inducer of certain CYP450s or P-glycoprotein). Certain models have been developed to predict potential herb–drug interactions, using pharmacokinetic principles.[16]

It is important to note that herb–drug interactions are likely to be under-reported. Currently, only a small number of drugs and herbs have been tested in clinical trials for potential interactions. Chinese medicine practitioners and physicians should examine prescribed drugs and herbal formulations/products to identify whether any ingredients of concern are involved. They should also monitor clinical signs of the patients for any changes in responses or side effects of administered drugs after taking herbal medicines. The general advice is to avoid the concurrent use of drugs and herbal medicines in certain clinical conditions.

How to report herb–drug interactions in Australia

In Australia, all suspected drug interactions, including suspected adverse reactions to prescription medicines, vaccines, over-the-counter and complementary medicines, should be reported to the Adverse Drug Reactions Unit at the Therapeutic Goods

TABLE 1 Reported Herb–Drug Interactions in Humans

Herb (Latin name)	Drug	Evidence	Reference
St John's Wort (*Hypericum perforatum*)	Cyclosporin	Case reports	19–27, 31–34
		Case series	35, 36
		Clinical trial	37
	Sertraline	Case reports	38, 39
	Oral contraceptives	Case series	40. 41
		Clinical trials	42, 43
	Paroxetine	Case report	44
	Theophylline	Case report	6
	Loperamide	Case report	45
	Nefazodone	Case report	38
	Phenpro-coumon	Case report	34
	Venlaxafine	Case report	46
	Amitriptylin	Clinical trial	47
	Tacrolimus	Clinical trials	48, 49
	Simvastatin	Clinical trial	50
	Imatinib	Clinical trial	51
	Indinavir	Clinical trial	52
	Irenotecan	Clinical trial	53
	R- and S- verapamil	Clinical trial	54
	Midazolam	Clinical trial	55
	Digoxin	Clinical trials	4, 56, 57
	Fexofenadine	Clinical trials	58
	Warfarin	Clinical trial	59
		Case series	5
Ginseng (*Panax* species)	Phenelzine	Case reports	60, 61
	Warfarin	Case reports	62, 63
		Clinical trials	59, 64
American Ginseng**	Warfarin	Clinical trial	65
Siberian ginseng (*Eleutherococcus senticosis*)	Digoxin	Case report	66
Danshen (*Salvia miltiorrhiza*)	Warfarin	Case reports	18, 67, 68
Dang gui (*Angelica sinensis*)	Warfarin	Case reports	69, 70
Papaya extract (*Papaya carica*)	Warfarin	Case report	71
Devil's claw (*Harpagophytum procumbens*)	Warfarin	Case report	71

TABLE 1 Continued

Herb (Latin name)		Drug	Evidence	Reference
Garlic (*Allium sativum*)		Warfarin	Case report	72
		Saquinavir	Clinical trial	73
		Alprazolam	Clinical trial	74
Ginkgo (*Ginkgo biloba*)		Warfarin	Clinical trials*	64, 75, 76
		Warfarin	Case report	77
		Trazodone	Case report	78
		Valerian	Case report	79
		Thiazide diuretic	Case report	80
		Aspirin	Case report	81
		Ibuprofen	Case report	82
		Phenytoin	Case report	83
		Omeprazole	Clinical trial	84
Kava (*Piper methysticum*)		Alprazolam	Case report	85
		Levodopa	Case report	86
Betel nut (*Areca catechu*)		Flupenthixol	Case report	87
		Fluphenazine	Case report	87
Gan Cao**		Digitalis	Case report	88
		Enalapril	Case report	89
Chilli pepper (*Capsicum* species)		ACE inhibitor	Case report	90
FORMULAS	Xiao Chai Hu Tang (sho-saiko-to)	Caffeine	Clinical trial	91
		Prednisolone	Clinical trial	92
	Saiboku-To	Prednisolone	Clinical trial	92
	Sairei-To	Prednisolone	Clinical trial	92

Notes: All clinical trials included in the table demonstrated significant herb–drug interactions, except the one marked with *, which showed no significant interaction between Warfarin and Ginkgo. ** Indicates that the Latin name was not given in the relevant study, meaning that the herb species could not be identified with certainty by the authors of this review.

Administration (TGA) (www.tga.gov.au/adr). Reports can be made electronically at www.tgasime.health.gov.au, or by using the 'Blue Card' pre-paid reporting form (available from www.tga.gov.au/adr), or by calling the Consumer Adverse Medication Events Line (telephone: 1300 134 237). The information to be included in a report is the patient's details, a description of the suspected reaction and medicines involved, as well as any treatment and outcome details (refer to the Blue Card for an information check-list). For complementary medicines, it will be useful to include product information such as AUST L number if possible.

Conclusion

Herb–drug interaction is an important issue affecting the efficacy and safety of therapeutic treatments. Chinese herbal medicine practitioners should have adequate knowledge in this area and adopt proper strategies to monitor and report potential herb–drug interactions in order to minimise harmful adverse reactions and improve the efficacy of Chinese herbal medicines.

References

1. MacLennan AH, Myers SP, Taylor AW. The continuing use of complementary and alternative medicine in South Australia: costs and beliefs in 2004. Med J Aust 2006;184(1):27–31.
2. Expert Committee on Complementary Medicines in the Health System. Complementary Medicines in the Australian Health System. Canberra: Commonwealth of Australia; 2003.
3. Kuhn MA. Herbal remedies: drug–herb interactions. Crit Care Nurse 2002;22(2):22–35.
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(4):338–45.
5. Yue QY, Bergquist C, Gerden B. Safety of St John's wort (*Hypericum perforatum*). Lancet 2000;355(9203):576–7.
6. Nebel A, Schneider BJ, Baker RK, Kroll DJ. Potential metabolic interaction between St John's wort and theophylline. Ann Pharmacother 1999;33(4):502.
7. Mok T, Yeo W, Johnson P, Hui P, Ho W, Lam K et al. A double-blind placebo-controlled randomized study of Chinese herbal medicine as complementary therapy for reduction of chemotherapy-induced toxicity. Ann Oncol 2007;18(4):768–74.
8. Li CG, Monyle K, Xue C. Problems and challenges with Chinese herbal medicine. In: Leung P, Xue C, Cheng Y, editors. A comprehensive guide to Chinese medicine. Singapore: World Scientific; 2003. p. 85–112.
9. Mathewson Kuhn M. Pharmacotherapeutics: a nursing process approach. 4th ed. Philadelphia: FA Davis; 1998.
10. Klepser TB, Doucette WR, Horton MR, Buys LM, Ernst ME, Ford JK et al. Assessment of patients' perceptions and beliefs regarding herbal therapies. Pharmacotherapy 2000;20(1):83–7.
11. Wooltorton E, Sibbald B. Ephedra/ephedrine: cardiovascular and CNS effects. CMAJ 2002;166(5):633.
12. Yang XX, Hu ZP, Duan W, Zhu YZ, Zhou SF. Drug–herb interactions: eliminating toxicity with hard drug design. Curr Pharm Des 2006;12(35):4649–64.
13. Yoshida N, Koizumi M, Adachi I, Kawakami J. Inhibition of P-glycoprotein-mediated transport by terpenoids contained in herbal medicines and natural products. Food Chem Toxicol 2006;44(12):2033–9.
14. Block KI, Gyllenhaal C. Clinical corner: herb–drug interactions in cancer chemotherapy: theoretical concerns regarding drug metabolizing enzymes. Integr Cancer Ther 2002;1(1):83–9.
15. Nebert DW, Nelson DR, Coon MJ, Estabrook RW, Feyereisen R, Fujii-Kuriyama Y et al. The P450 superfamily: update on new sequences, gene mapping, and recommended nomenclature. DNA Cell Biol 1991;10(1):1–14.
16. Zhou S, Huang M, Xu A, Yang H, Duan W, Paxton JW. Prediction of herb–drug metabolic interactions: a simulation study. Phytother Res 2005;19(6):464–71.
17. Heck AM, DeWitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. Am J Health Syst Pharm 2000;57(13):1221–30.
18. Yu CM, Chan JC, Sanderson JE. Chinese herbs and warfarin potentiation by 'danshen'. J Intern Med 1997;241(4):337–9.
19. Barone GW, Gurley BJ, Ketel BL, Lightfoot ML, Abul-Ezz SR. Drug interaction between St John's wort and cyclosporine. Ann Pharmacother 2000;34(9):1013–16.
20. Mai I, Kruger H, Budde K, Johne A, Brockmoller J, Neumayer HH et al. Hazardous pharmacokinetic interaction of Saint John's wort (*Hypericum perforatum*) with the immunosuppressant cyclosporin. Int J Clin Pharmacol Ther 2000;38(10):500–2.
21. Karliova M, Treichel U, Malago M, Frilling A, Gerken G, Broelsch CE. Interaction of *Hypericum perforatum* (St John's wort) with cyclosporin A metabolism in a patient after liver transplantation. J Hepatol 2000;33(5):853–5.
22. Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to Saint John's wort. Lancet 2000;355(9203):548–9.
23. Moschella C, Jaber BL. Interaction between cyclosporine and Hypericum perforatum (St John's wort) after organ transplantation. Am J Kidney Dis 2001;38(5):1105–7.
24. Turton-Weeks SM, Barone GW, Gurley BJ, Ketel BL, Lightfoot ML, Abul-Ezz SR. St John's wort: a hidden risk for transplant patients. Prog Transplant 2001;11(2):116–20.
25. Ahmed SM, Banner NR, Dubrey SW. Low cyclosporin: a level due to Saint John's wort in heart transplant patients. J Heart Lung Transplant 2001;20(7):795.
26. Beer AM, Ostermann T. [St John's wort: interaction with cyclosporine increases risk of rejection for the kidney transplant and raises daily cost of medication]. Med Klin (Munich) 2001;96(8):480–3.
27. Alscher DM, Klotz U. Drug interaction of herbal tea containing St John's wort with cyclosporine. Transpl Int 2003;16(7):543–4.
28. 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(2):167–74.
29. Chen MF, Shimada F, Kato H, Yano S, Kanaoka M. Effect of glycyrrhizin on the pharmacokinetics of prednisolone following low dosage of prednisolone hemisuccinate. Endocrinol Jpn 1990;37(3):331–41.
30. Teelucksingh S, Mackie AD, Burt D, McIntyre MA, Brett L, Edwards CR. Potentiation of hydrocortisone activity in skin by glycyrrhetinic acid. Lancet 1990;335(8697):1060–3.
31. Barone GW, Gurley BJ, Ketel BL, Abul-Ezz SR. Herbal supplements: a potential for drug interactions in transplant recipients. Transplantation 2001;71(2):239–41.
32. Rey JM, Walter G. *Hypericum perforatum* (St John's wort) in depression: pest or blessing? Med J Aust 1998;169(11–12):583–6.
33. Bon S, Hartmann K, Johanniskraut KM. Ein Enzyminduktor? Schweiz Apoth Ztg 1999;16:535–6.
34. Gordon JB. SSRIs and St John's wort: possible toxicity? Am Fam Physician 1998;57(5):950–3.
35. Breidenbach T, Hoffmann MW, Becker T, Schlitt H, Klempnauer J. Drug interaction of St John's wort with cyclosporin. Lancet 2000;355(9218):1912.
36. 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(10):2229–30.
37. 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(2):203–11.
38. Lantz MS, Buchalter E, Giambanco V. St John's wort and antidepressant drug interactions in the elderly. J Geriatr Psychiatry Neurol 1999;12(1):7–10.

39. Barbenel DM, Yusufi B, O'Shea D, Bench CJ. Mania in a patient receiving testosterone replacement postorchidectomy taking St John's wort and sertraline. J Psychopharmacol 2000;14(1):84–6.
40. Ratz AE, von Moos M, Drewe J. [St John's wort: a pharmaceutical with potentially dangerous interactions]. Schweiz Rundsch Med Prax 2001;90(19):843–9.
41. Schwarz UI, Buschel B, Kirch W. Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception. Br J Clin Pharmacol 2003;55(1):112–3.
42. Hall SD, Wang Z, Huang SM, Hamman MA, Vasavada N, Adigun AQ et al. The interaction between St John's wort and an oral contraceptive. Clin Pharmacol Ther 2003;74(6):525–35.
43. Murphy PA, Kern SE, Stanczyk FZ, Westhoff CL. Interaction of St John's wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. Contraception 2005;71(6):402–8.
44. Waksman JC, Heard K, Jolliff H, Daly FFS, Bogdan GM, Dart RC. Serotonin syndrome associated with the use of St John's wort (*Hypericum perforatum*) and paroxetine [Abstract]. Clin Toxicol 2000;38(5):521.
45. Khawaja IS, Marotta RF, Lippmann S. Herbal medicines as a factor in delirium. Psychiatr Serv 1999;50(7):969–70.
46. Prost N, Tichadou L, Rodor F, Nguyen N, David JM, Jean-Pastor MJ. [St Johns wort–venlafaxine interaction]. Presse Med 2000;29(23):1285–6.
47. Johne A, Schmider J, Brockmoller J, Stadelmann AM, Stormer E, Bauer S et al. Decreased plasma levels of amitriptyline and its metabolites on comedication with an extract from St John's wort (*Hypericum perforatum*). J Clin Psychopharmacol 2002;22(1):46–54.
48. 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(1):89–94.
49. 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(4):819–22.
50. 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(6):518–24.
51. Frye RF, Fitzgerald SM, Lagattuta TF, Hruska MW, Egorin MJ. Effect of St John's wort on imatinib mesylate pharmacokinetics. Clin Pharmacol Ther 2004;76(4):323–9.
52. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. Lancet 2000;355(9203):547–8.
53. Mathijssen RH, Verweij J, de Bruijn P, Loos WJ, Sparreboom A. Effects of St John's wort on irinotecan metabolism. J Natl Cancer Inst 2002;94(16):1247–9.
54. Tannergren C, Engman H, Knutson L, Hedeland M, Bondesson U, Lennernas H. St John's wort decreases the bioavailability of R- and S-verapamil through induction of the first-pass metabolism. Clin Pharmacol Ther 2004;75(4):298–309.
55. Mueller SC, Majcher-Peszynska J, Uehleke B, Klammt S, Mundkowski RG, Miekisch W et al. The extent of induction of CYP3A by St John's wort varies among products and is linked to hyperforin dose. Eur J Clin Pharmacol 2006;62(1):29–36.
56. Durr D, Stieger B, Kullak-Ublick GA, Rentsch KM, Steinert HC, Meier PJ et al. St John's wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. Clin Pharmacol Ther 2000;68(6):598–604.
57. Mueller SC, Uehleke B, Woehling H, Petzsch M, Majcher-Peszynska J, Hehl EM et al. Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin. Clin Pharmacol Ther 2004;75(6):546–57.
58. Wang Z, Hamman MA, Huang SM, Lesko LJ, Hall SD. Effect of St John's wort on the pharmacokinetics of fexofenadine. Clin Pharmacol Ther 2002;71(6):414–20.
59. Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC et al. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 2004;57(5):592–9.
60. Shader RI, Greenblatt DJ. Phenelzine and the dream machine: ramblings and reflections. J Clin Psychopharmacol 1985;5(2):65.
61. Jones BD, Runikis AM. Interaction of ginseng with phenelzine. J Clin Psychopharmacol 1987;7(3):201–2.
62. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Health Syst Pharm 1997;54(6):692–3.
63. Rosado MF. Thrombosis of a prosthetic aortic valve disclosing a hazardous interaction between warfarin and a commercial ginseng product. Cardiology 2003;99(2):111.
64. Jiang X, Blair EY, McLachlan AJ. Investigation of the effects of herbal medicines on warfarin response in healthy subjects: a population pharmacokinetic–pharmacodynamic modeling approach. J Clin Pharmacol 2006;46(11):1370–8.
65. Yuan CS, Wei G, Dey L, Karrison T, Nahlik L, Maleckar S et al. American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial [Brief communication]. Ann Intern Med 2004;141(1):23–7.
66. McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. CMAJ 1996;155(3):293–5.
67. Tam LS, Chan TY, Leung WK, Critchley JA. Warfarin interactions with Chinese traditional medicines: danshen and methyl salicylate medicated oil. Aust NZ J Med 1995;25(3):258.
68. Izzat MB, Yim AP, El-Zufari MH. A taste of Chinese medicine! Ann Thorac Surg 1998;66(3):941–2.
69. Page RL, 2nd, Lawrence JD. Potentiation of warfarin by dong quai. Pharmacotherapy 1999;19(7):870–6.
70. Ellis GR, Stephens MR. Untitled (photograph and brief case report). In 'Minerva'. BMJ 1999;319(7210):650.
71. Shaw D, Leon C, Kolev S, Murray V. Traditional remedies and food supplements: a 5-year toxicological study (1991–1995). Drug Saf 1997;17(5):342–56.
72. Sunter WH. Warfarin and garlic [Letter]. Pharm J 1991;246:722.
73. Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. Clin Infect Dis 2002;34(2):234–8.
74. Markowitz JS, Devane CL, Chavin KD, Taylor RM, Ruan Y, Donovan JL. Effects of garlic (*Allium sativum* L.) supplementation on cytochrome P450 2D6 and 3A4 activity in healthy volunteers. Clin Pharmacol Ther 2003;74(2):170–7.
75. Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 2005;59(4):425–32.

76. Engelsen J, Nielsen JD, Hansen KF. [Effect of coenzyme Q10 and *Ginkgo biloba* on warfarin dosage in patients on long-term warfarin treatment. A randomized, double-blind, placebo-controlled cross-over trial]. Ugeskr Laeger 2003;165(18):1868–71.

77. Matthews MK, Jr. Association of *Ginkgo biloba* with intracerebral hemorrhage. Neurology 1998;50(6):1933–4.

78. Galluzzi S, Zanetti O, Binetti G, Trabucchi M, Frisoni GB. Coma in a patient with Alzheimer's disease taking low dose trazodone and *Gingko biloba*. J Neurol Neurosurg Psychiatry 2000;68(5):679–80.

79. Chen D, Klesmer J, Giovanniello A, Katz J. Mental status changes in an alcohol abuser taking valerian and *Gingko biloba*. Am J Addict 2002;11(1):75–7.

80. Izzo AA, Di Carlo G, Borrelli F, Ernst E. Cardiovascular pharmacotherapy and herbal medicines: the risk of drug interaction. Int J Cardiol 2005;98(1):1–14.

81. Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract. N Engl J Med 1997;336(15):1108.

82. Meisel C, Johne A, Roots I. Fatal intracerebral mass bleeding associated with *Ginkgo biloba* and ibuprofen. Atherosclerosis 2003;167(2):367.

83. Kupiec T, Raj V. Fatal seizures due to potential herb–drug interactions with *Ginkgo biloba*. J Anal Toxicol 2005;29(7):755–8.

84. Yin OQ, Tomlinson B, Waye MM, Chow AH, Chow MS. Pharmacogenetics and herb–drug interactions: experience with *Ginkgo biloba* and omeprazole. Pharmacogenetics 2004;14(12):841–50.

85. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. Ann Intern Med 1996;125(11):940–1.

86. Schelosky L, Raffauf C, Jendroska K, Poewe W. Kava and dopamine antagonism. J Neurol Neurosurg Psychiatry 1995;58(5):639–40.

87. Deahl M. Betel nut-induced extrapyramidal syndrome: an unusual drug interaction. Mov Disord 1989;4(4):330–2.

88. Harada T, Ohtaki E, Misu K, Sumiyoshi T, Hosoda S. Congestive heart failure caused by digitalis toxicity in an elderly man taking a licorice-containing Chinese herbal laxative. Cardiology 2002;98(4):218.

89. Iida R, Otsuka Y, Matsumoto K, Kuriyama S, Hosoya T. Pseudoaldosteronism due to the concurrent use of two herbal medicines containing glycyrrhizin: interaction of glycyrrhizin with angiotensin-converting enzyme inhibitor. Clin Exp Nephrol 2006;10(2):131–5.

90. Hakas JF, Jr. Topical capsaicin induces cough in patient receiving ACE inhibitor. Ann Allergy 1990;65(4):322–3.

91. Saruwatari J, Nakagawa K, Shindo J, Nachi S, Echizen H, Ishizaki T. The in-vivo effects of sho-saiko-to, a traditional Chinese herbal medicine, on two cytochrome P450 enzymes (1A2 and 3A) and xanthine oxidase in man. J Pharm Pharmacol 2003;55(11):1553–9.

92. Homma M, Oka K, Ikeshima K, Takahashi N, Niitsuma T, Fukuda T et al. Different effects of traditional Chinese medicines containing similar herbal constituents on prednisolone pharmacokinetics. J Pharm Pharmacol 1995;47(8):687–92.