



## Review

# Pharmacodynamic and pharmacokinetic interactions between herbs and western drugs

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## SUMMARY

In recent years, the combined use of Herbal medicines and Western drugs has been increasing. Though certain problems may occur when both types of medicines are taken together, they have not been adequately analyzed. It was reported that anticoagulation was enhanced in addition to bleeding when patients took long-term warfarin therapy in combination with *Salvia miltiorrhiza* (danshen), and laxative herbs accelerate intestinal transit and interfere with the absorption. Herbal constituents, curcumin, ginsenosides, piperine, catechins and silymarin were found to be inhibitors of P-glycoprotein. St John's wort induces the intestinal expression of P-glycoprotein. Anthraquinone, quercetin and coumarins were found to be a potent inhibitor of P-450. Glycyrrhizin or liquorice extracts, Garlic and St John's wort are a potent inducer of CYP3A4. This review provides a critical overview of interactions between herbal medicines and other drugs. Hence, it is necessary to study the pharmacodynamic and pharmacokinetic interactions of many herbal medicines between western drugs

**Key words:** Herbal medicine; Drug interaction; Pharmacokinetic; Pharmacodynamic; P-glycoprotein; P-450; CYP3A4

## INTRODUCTION

Herbs and preparations have been used to treat ailments since medicine began. The treatment of diseases with medicines of plant origin is an integral part of many cultures throughout the world. The most ancient plants thought to be of medical significance were discovered in prehistoric graves and are 60,000 years old. In recent years, the combined use of Herbal medicines and Western

drugs has been increasing. Though certain problems may occur when both types of medicines are taken together, they have not been adequately analyzed. It is reported that some of herbal medicines such as St. John's wort, garlic, ginseng, and ginkgo, have given rise to clinical interactions when co-administered with prescription medicines. Such adversities have spurred various pre-clinical and *in vitro* investigations on a series of other herbal remedies. In this review, pharmacokinetic and pharmacodynamic studies that have been conducted for some of more important or widely used phytopharmaceuticals are critically evaluated. Furthermore, various drug interactions are discussed, showing that caution should be

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exercised when combining phytopharmaceuticals with chemically derived active pharmaceutical ingredients.

### **Drug interactions between herbal and prescription medicines**

Interactions between herbal and prescription medications may be caused by either pharmacodynamic or pharmacokinetic mechanism. Pharmacodynamic interactions may occur when constituents of herbal products have either synergistic or antagonist activity in relation to conventional drugs. As a result, concentration-dependent activity of a therapeutic molecule is altered on the site of action at the drug-receptor level. Pharmacokinetic interactions result from alteration of absorption, distribution, metabolism, or elimination of a conventional drug by a herbal product or other dietary supplements. To date, several pharmacokinetic drug-herb interactions (absorption, distribution, and metabolism) and additive pharmacodynamic interactions have been identified.

### **Pharmacodynamic interactions**

Pharmacodynamic interactions can occur when a herbal product produces additive, synergistic, or antagonist activity in relation to the conventional drug with no change in the plasma concentration of either herbal product or drug. Pharmacodynamic interactions are related to the pharmacologic activity of interacting agents and can affect organ systems, receptor sites, or enzymes. A pharmacodynamic interaction may occur when herbals that possess antiplatelet activity are administered with anticoagulant drugs, thus increasing the risk of bleeding. The anticoagulant action of warfarin is enhanced by ginkgo (*Ginkgo biloba*) and possibly by many other herbs, such as Danshen (*Salvia miltorrhiza*), Dong quai (*Angelica sinensis*), Galic (*Allium sativum*) and *Panax Ginseng* (Fugh-berman and Ernst, 2001). Regarding effects of angelica root with warfarin, angelica root affects not the pharmacokinetics but

the pharmacodynamics in rabbits (Lo *et al.*, 1995; Page and Lawrence, 1999). Other examples of animal studies with barbiturates, pentobarbital and hexobarbital, and other non-barbiturate CNS-depressants like urethane and glutethimide suggest not simply additive but synergistic effects with kavalactones (Klohs *et al.*, 1959; Meyer, 1962; Jennifer and Ramzana, 2004), and *G. biloba* may act as an antagonist on gamma-aminobutyric acid (GABA) activity at benzodiazepine binding sites (Huang *et al.*, 2004; Mary *et al.*, 2006).

### **Pharmacokinetic interactions**

Pharmacokinetic herb-drug interactions are due to altered absorption, metabolism, distribution and excretion of drugs. The primary mechanism of absorption is passive diffusion of nonionized drug molecules via the lipophilic gastrointestinal (GI) mucosa. Therefore, drugs that change pH, gastric emptying time, or GI motility will interact with the absorption of other agents. The most popular stimulant laxative herbs of the anthranoid-containing senna (*Cassia senna* and *C. angustifolia*), cascara sagrada (*Rhamnus purshiana*), aloe vera (*Aloe barbadensis*), frangula (*Rhamnus frangula*), yellow dock (*Rumex crispus*), and Chinese rhubarb (*Rheum officinale*) will accelerate intestinal transit, and thus may interfere with the absorption of almost any intestinally absorbed drugs (Westendorf; Adriane, 2000). It is well-known that metal ions and tannic acid present in herbal medicine form insoluble chelates or complexes with some western drugs such as antibiotics, isoniazid and levodopa, resulting in reduction of drug absorption (Chan and Cheung, 2000). It is also reported that alkaloids or other flavonoids form precipitates with some western drugs containing aluminium, bismuth, calcium, ferrous and magnesium ions. More recently, induction and inhibition of intestinal P-glycoprotein have been described in significant drug interactions. The P-glycoprotein drug transporter is a glycoprotein encoded by the MDR1 gene and functions as a transmembrane efflux transporter that pumps

**Table 1.** Pharmacodynamic interaction between herbal and prescription medicines

Herb	Drug	Result of interaction	Mechanism	
Ginko	Aspirin	Spontaneous hyphema	Additive effect on platelet aggregation	(Matthews, 1998)
	Warfarin	Over - anticoagulation	Additive effect on coagulation mechanism	(Matthews, 1998)
Ginger	Phenprocoumon	Over - anticoagulation	Additive effect on coagulation	(Kruth <i>et al.</i> , 2004)
Danshen				(Yu <i>et al.</i> , 1997)
Ding quai				(Page <i>et al.</i> , 1999)
Galic			Additive effect on coagulation mechanism	(Sunter, 1991)
Ginseng	Warfarin	Over - anticoagulation		(Rosado, 2003; Jiang <i>et al.</i> , 2004; Janetzky <i>et al.</i> , 1997)
Curbicin			Curbicin containing vit E, which can antagonize vit K	(Yue <i>et al.</i> , 2001).
Green tea		Decreased anticoagulant effect	Green tea containing vit E, which can antagonize warfarin	(Taylor <i>et al.</i> , 1999)
Kava	Alprazolam	Semicomatose state	Additive effect on GABA receptors	(Almeida <i>et al.</i> , 1996).
	Levodopa	Reduced efficacy of levodopa	Kava possessing dopaminergic antagonistic properties	(Schelosky <i>et al.</i> , 1995)
St john's wort	SRI (serotonin-reuptake inhibitor-sertraline, paroxetine, nefazodone and venlafaxin)	Serotonergic syndrome	Synergistic effect on 5-HT uptake	(Gordon <i>et al.</i> , 1998; Lantz <i>et al.</i> , 1999; Prost <i>et al.</i> , 2000)
	Buspiron	Hyponania	Synergistic effect on 5-HT receptors	(Dannawi <i>et al.</i> , 2002)

drugs out of cells (Zhou *et al.*, 2004). P-glycoproteins are found in many tissues and especially in organs responsible for drug absorption or elimination, such as the intestine, liver, and kidneys (Horn *et al.*, 2002). P-glycoprotein is vulnerable to inhibition, activation, or induction by herbs and herbal constituents. Curcumin, ginsenosides, piperine, some catechins from green tea, and silymarin from milk thistle were found to be inhibitors of P-glycoprotein (Zhou *et al.*, 2004). St John's wort induces the intestinal expression of P-glycoprotein (Izzo, 2004). Drug metabolism is divided into 2 categories of phase I and phase II transformation reactions. Phase I reactions include oxidation, hydrolysis, and reduction, resulting in a compound that is generally less toxic and more hydrophilic, allowing for easy excretion. Phase II reactions primarily result in termination of biologic activity

of the drug. Phase II transformation reactions include glucuronidation, sulfation, acetylation, and methylation (Shannon *et al.*, 2005). The CYP450 is the most important phase I drug-metabolizing enzyme system and it is a family of monooxygenase enzymes that are mainly found in intestinal and liver cells and catalyzes several Phase I metabolic processes including oxidation, hydroxylation, S- and O-demethylation, and oxidative deamination. Many herbs and natural compounds isolated from herbs (e.g., flavonoids, coumarins, furanocoumarins, anthraquinones, caffeine and terpenes) have been identified as substrates, inhibitors or inducers of various CYP enzymes (Ioannides, 2002) (Table 2).

Induction of CYP450 enzymes occurs when a drug stimulates the synthesis of more enzyme proteins, enhancing the enzyme's metabolizing capacity. In studies conducted with mice, glycyrrhizin

**Table 2.** Pharmacokinetic interaction between herbal and prescription medicines

Herb	Drug	Result of interaction	Mechanism	
St john's wort	Digoxin	Decreased plasma digoxin concentration	St john's wort induces p-glycoprotein involved in digoxin absorption and excretion.	(Johne <i>et al.</i> , 1999; Mueller <i>et al.</i> , 2004; Huupponen <i>et al.</i> , 1984; Nordstrom <i>et al.</i> , 1987)
	Simvastatin	Decreased plasma digoxin concentration	Simvastatin is a substrate of p-glycoprotein and metabolized by CYP enzymes. Both CYP enzymes and p-glycoprotein are induced by St john's wort.	(Sugimoto <i>et al.</i> , 2001)
	Warfarin	Decreased anticoagulant effect	Warfarin is metabolized by CYP enzymes which are induced by St john's wort.	(Jiang <i>et al.</i> , 2004)
	Phenprocoumon	Decreased anticoagulant effect	Phenprocoumon is metabolized by CYP enzymes which are induced by St john's wort.	(Maurer <i>et al.</i> , 1999; Mueller <i>et al.</i> , 2004)
	Verapamil	Decreased bioavailability of verapamil	Induction of intestinal CYP3A4 by St john's wort	(Tannergren <i>et al.</i> , 2004)
	Alprazolam	Decreased plasma levels of alprazolam	Alprazolam is specific probe for CYP3A4 induced by St john's wort.	(Markowitz <i>et al.</i> , 2003; Markowitz <i>et al.</i> , 2004)
Kaba	Alprazolam	Semicomatose state	Kaba inhibits CYP3A	(Almeida <i>et al.</i> , 1996)
Cranberry	Warfarin	Over - anticoagulation	Cranberry flavonoids CYP enzyme	(Grant P, 2004)
Echinacea	Midazolam	Decreased systemic midazolam clearance	Echinacea inhibits intestinal CYP3A4.	(Gorski <i>et al.</i> , 2004)
	Caffeine	Decreased caffeine oral clearance	Caffeine is a substrate of CYP which is inhibited by Echinacea	
Grapefruit juice	Nifedipine	Decreased systemic clearance	Furanocoumarines inhibit CYP enzyme.	(Mohri <i>et al.</i> , 2001)
	Cyclosporin			(Yee <i>et al.</i> , 1995)
	Felodipine			(Bailey <i>et al.</i> , 2000)

or liquorice (*Glycyrrhiza uralensis*) extracts elevated the metabolism of diagnostic substrates associated with CYP3A, and increased the activity of CYP2B, CYP1A2 and CYP2A1 (Paolini *et al.*, 1999). Garlic may induce hepatic CYP3A4 metabolism of saquinavir resulting in decreased plasma drug levels (Piscitelli *et al.*, 2002). St John's wort (*Hypericum perforatum*) is a potent inducer of CYP3A4 and involved in the most severe drug-herb interactions. The protease inhibitors, cyclosporine, warfarin, digoxin, oral contraceptives, and many other medications can be rendered ineffective with concomitant use of St John's wort (Zhou *et al.*, 2004). Inhibition of CYP450 enzymes may occur secondary to competitive binding between two drugs or to permanent inactivation (Shannon, 2005). Generally, inhibition begins after the first dose of the inhibitor and the length of inhibition correlates with the half-life of the drug.

Discontinuation of the inhibitor will usually cause a decreased serum concentration of other drugs metabolized by that enzyme, whereas discontinuation of an inducer will result in an increased serum concentration and risk of toxicity. *In vitro* investigations, commercial ethanolic extracts of many herbs extensively inhibit the CYP3A4-mediated debenzoylation of benzyloxyresorufin (Budzinski *et al.*, 2000). Similarly, hot water decoctions or 40% ethanol infusions of many herbal remedies impair CYP3A activity (Guo *et al.*, 2001). The phytochemical anthraflavic acid, a planar anthraquinone, is a potent inhibitor of hepatic CYP1A activity *in vitro* (Ayrton *et al.*, 1987). Quercetin was found to be a potent inhibitor of CYP-450 (Breinholt *et al.*, 1999; Sousa and Marletta, 1985). Inhibitory effects of quercetin on CYP1A2 and CYP2C8 have been reported (Dierks *et al.*, 2001). Coumarins, which are

contained in grapefruits, effectively and selectively inhibit and inactivate several cytochrome P450 enzymes (Cai *et al.*, 1993). The furanocoumarins such as notopterol and paradisins were reported to inhibit a specific human drug metabolizing enzyme, cytochrome P450 3A (CYP3A) from activity (Mäenpää *et al.*, 1993; Guo *et al.*, 2000). Grapefruit juice has been found to significantly increase oral bioavailability of most dihydropyridines (e.g., felodipine), terfenadine, saquinavir, cyclosporine, midazolam, triazolam and verapamil (Yee *et al.*, 1995; He *et al.*, 1998; Bailey *et al.*, 2000; Mohri and Uesawa, 2001; Ioannides, 2001). A new CYP3A4 inhibitor, paradisin C, was recently isolated from grapefruit juice (Ohta *et al.*, 2002). These results, therefore, raised the concern that the furanocoumarin containing oriental medicines may alter pharmacokinetics of co-ingested drugs similar to the case with grapefruit juice. The hot-water extract of *Angelica dahurica* root (*Angelica dahurica* Benth. et Hook.) exhibited the potential to affect the metabolism of other drugs by liver cytochrome P450 (Ishihara *et al.*, 2000).

### Conclusions and future prospects

Cases have been published reporting enhanced anticoagulation and bleeding when patients took long-term warfarin therapy in combination with *Salvia miltiorrhiza* (danshen). Laxative herbs, anthranoid contained in senna, cascara sagrada, aloe vera, frangula, yellow dock, and Chinese rhubarb (*Rheum officinale*) will accelerate intestinal transit, and thus may interfere with the absorption of almost any intestinally absorbed drugs. It is well-known that metal ions and tannic acid present in herbal medicine form insoluble chelates or complexes with some western drugs such as antibiotics, isoniazid and levodopa, resulting in reduction of drug absorption. P-glycoprotein appears to limit the cellular transport from intestinal lumen into epithelial cells and also enhances the excretion of drugs out of hepatocytes and renal tubules into the adjacent luminal space. Curcumin, ginsenosides,

piperine, catechins, and silymarin were found to be inhibitors, but St John's wort is an inducer of P-glycoprotein. The CYP450 is the most important phase I drug-metabolizing enzyme system. Glycyrrhizin or liquorice extracts, garlic and St John's wort are potent inducers of CYP3A4. Ethanolic extracts of many herbs extensively inhibit the CYP3A4. *Angelica dahurica* root and herbal constituents of anthraquinone, quercetin, coumarins, and furanocoumarin inhibit and inactivate a number of cytochrome P450 enzymes.

An extensive review of the literature identified the reported herb-drug interactions with clinical significance, many of which are from case reports and limited clinical observations. The interactions mentioned above make up merely a small percentage of possible drug interactions. A lot of work is still required to be done in systematic investigations for the interactions between herbal and modern drugs. Hence, it is necessary to study the pharmacodynamic and pharmacokinetic interactions of many herbal medicines between western drugs to identify the safety, the efficacy or risk of side effects in clinical use.

### REFERENCES

- Adriane FB. (2000) Herb-drug interactions. *Lancet* **355**, 134-138.
- Almeida JC, Grimsley EW. (1996) Coma from the health food store: interaction between kava and alprazolam. *Ann. Intern. Med.* **125**, 940-941.
- Angelo A Izzo. (2004) Herb-drug interactions: an overview of the clinical evidence. *Fundam Clin. Pharmacol.* **19**, 1-16.
- Ayrton AD, Lewis DFV, Ioannides C, Walker R. (1987) Anthraflavic acid is a potent and specific inhibitor of cytochrome P-448 activity. *Biochim. Biophys. Acta* **916**, 328-333.
- Bailey DG, Dresser GK, Kreeft JH, Munoz C, Freeman DJ, Bend JR. (2000) Grapefruit felodipine interaction: effect of unprocessed fruit and probable active ingredients. *Clin. Pharmacol. Ther.* **68**, 468-477.
- Breinholt V, Lauridsen ST, Dragsted LO. (1999) Differential effects of dietary flavonoids on drug

- metabolizing and antioxidant enzymes in female rat. *Xenobiotica* **29**, 1227-1240.
- Budzinski JW, Foster BC, Vandenhoeck S, Arnason JT. (2000) An *in vitro* evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. *Phytomedicine* **7**, 273-282.
- Cai Y, Bennett D, Nair RV, Ceska O, Ashwood-Smith MJ, Diiovanni J. (1993) Inhibition and inactivation of murine hepatic ethoxy- and pentoxyresorufin O-dealkylase by naturally occurring coumarins. *Chem. Res. Toxicol.* **6**, 872-879.
- Chan K, Cheung L. (2000) Examples of interactions between Chinese herbal medicinal products and orthodox drugs. In: *Interactions between Chinese Herbal Medicinal Products and Orthodox Drugs*. Harwood Academic Publishers, Amsterdam, Netherlands, 57-97.
- Dannawi M. (2002) Possible serotonin syndrome after combination of buspirone and St John's wort. *J. Psychopharmacol.* **16**, 401.
- Dierks EA, Stams KR, Lim HK, Cornelius G, Zhang H, Ball SE. (2001) A method for the simultaneous evaluation of the activities of seven major human drug-metabolizing cytochrome P450s using an *in vitro* cocktail of probe substrates and fast gradient liquid chromatography tandem mass spectrometry. *Drug Metab. Dispos.* **29**, 23-29.
- Fumio Ikegami, Yuichi Fujii, Tetsuo Satoh. (2004) Toxicological considerations of Kampo medicines in clinical use. *Toxicology* **198**, 221-228.
- Gordon JB. (1998) SSRIs and St John's wort: possible toxicity? *Am. Fam. Physician* **57**, 950.
- Gorski JC, Huang SM, Pinto A, Hamman MA, Hilligoss JK, Zaheer NA, Desai M, Miller M, Hall SD. (2004) The effect of echinacea (*Echinacea purpurea* root) on cytochrome P450 activity *in vivo*. *Clin. Pharmacol. Ther.* **75**, 89-100.
- Grant P. (2004) Warfarin and cranberry juice: an interaction. *J. Heart Valve Dis.* **13**, 25-26
- Guo LQ, Taniguchi M, Chen QY, Baba K, Yamazoe Y. (2001) Inhibitory potential of herbal medicines on human cytochrome P450-mediated oxidation: properties of umbelliferous or citrus crude drugs and their relative prescriptions. *Jpn. J. Pharmacol.* **85**, 399-408.
- Guo LQ, Taniguchi M, Xiao YQ, Baba K, Ohta T, Yamazoe Y. (2000) Inhibitory effect of natural furanocoumarin on human microsomal cytochrome P450 3A activity. *Jpn. J. Pharmacol.* **82**, 122-129.
- He K, Iyer KR, Hayes RN, Sinz MW, Woolf TF, Hollenberg PF. (1998) Inactivation of cytochrome P450 3A4 by bergamottin, a component of grapefruit juice. *Chem. Res. Toxicol.* **11**, 252-259.
- Horn JR, Hansten PD. (2002) Drug interactions: answers to frequently asked questions. *Pharm. Times* **68**, 67-78.
- Huang SH, Duke RK, Chebib M, Sasaki K, Wada K, Johnston GA. (2004) Ginkgolides, diterpene trilactones of *Ginkgo biloba*, as antagonists at recombinant  $\alpha 1\beta 2\gamma 2L$  GABAA receptors. *Eur. J. Pharmacol.* **494**, 131-138.
- Huupponen R, Seppala P, Iisalo E. (1984) Effect of guar gum, a fibre preparation, on digoxin absorption in man. *Eur. J. Clin. Pharmacol.* **26**, 279-281.
- Ioannides C. (2002) Pharmacokinetic interactions between herbal remedies and medicinal drugs. *Xenobiotica* **32**, 451-478.
- Ishihara K, Kushida H, Yuzurihara M, Wakui Y, Kitada M. (2000) Interaction of drugs and Chinese herbs, pharmacokinetic changes of tolbutamide and diazepam caused by extract of *Angelica dahurica*. *J. Pharm. Pharmacol.* **52**, 1023-1029.
- Janetzky K, Morreale AP. (1997) Probable interaction between warfarin and ginseng. *Am. J. Health Syst. Pharm.* **54**, 692-693.
- Jennifer A, Iqbal R. (2004) Pharmacokinetic and pharmacodynamic drug interactions with Kava (*Piper methysticum* Forst. f.). *J. Ethnopharmacol.* **93**, 153-160.
- Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO, McLachlan AJ. (2004) Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br. J. Clin. Pharmacol.* **57**, 592-599.
- Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I. (1999) Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clin. Pharmacol. Ther.* **66**, 338-345.
- Klohs MW, Keller F, Williams RE, Toekes MI, Gronheim GE. (1959) A chemical and pharmacological investigation of *Piper methysticum* Forst. *J. Med. Pharm. Chem.* **1**, 95-103.
- Kruth P, Brosi E, Fux R, Morike K, Gleiter CH. (2004)

- Ginger-associated overanticoagulation by phenprocoumon. *Ann Pharmacother.* **38**, 257-260.
- Lantz MS, Buchalter E, Giambanco V. (1999) St. John's wort and antidepressant drug interactions in the elderly. *J. Geriatr. Psychiatry Neurol.* **12**, 7-10.
- Lo ACT, Chan K, Yeung JHK, Woo KS. (1995) Danggui (*Angelica sinensis*) affects the pharmacodynamics but not the pharmacokinetics of warfarin in rabbits. *Eur. J. Drug Metab. Pharmacokinet.* **20**, 55-60.
- Markowitz JS, Donovan JL, DeVane CL, Taylor RM, Ruan Y, Wang JS, Chavin KD. (2003) Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *JAMA* **290**, 1500-1504.
- Markowitz JS, Donovan JL, DeVane CL, Taylor RM, Ruan Y, Wang JS, Chavin KD. (2004) Effect of St. John's wort on drug metabolism by induction of cytochrome p450 3A4 enzyme. *Obstet. Gynecol. Surv.* **59**, 358-359.
- Mary LC, Melanie AJ, Pedro IC. (2006) Evidence-based drug herbal interactions. *Life Sci.* **78**, 2146-2157.
- Matthews MK Jr. (1998) Association of *Ginkgo biloba* with intracerebral hemorrhage. *Neurology* **50**, 1933-1934.
- Maurer A, Johne A, Bauer S, Brockmoller J, Donath F, Roots I, Langheinrich M, Hubner WD. (1999) Interaction of St John's wort extract with phenprocoumon. *Eur. J. Clin. Pharmacol.* **55**, A22.
- Mäenpää J, Sigusch H, Raunio H, Syngelmä T, Vuorela P, Pelkonen O. (1993) Differential inhibition of coumarin 7-hydroxylase activity in mouse and human liver microsomes. *Biochem. Pharmacol.* **45**, 1035-1042.
- Meyer HJ. (1962) Pharmakologie der wirksamen prinzipien des Kawa-rhizoms (*Piper methysticum* Forst.). *Arch Int. Pharmacodyn. Ther.* **138**, 505-536.
- Mohri K, Uesawa Y. (2001) Effects of furanocoumarin derivatives in grapefruit juice on nifedipine pharmacokinetics in rats. *Pharm. Res.* **18**, 177-182.
- Mueller SC, Uehleke B, Woehling H, Petzsch M, Majcher-Peszynska J, Hehl EM, Sievers H, Frank B, Riethling AK, Drewelow B. (2004) Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin. *Clin. Pharmacol. Ther.* **75**, 546-557.
- Nordstrom M, Melander A, Robertsson E, Steen B. (1987) Influence of wheat bran and of a bulk-forming ispaghula cathartic on the bioavailability of digoxin in geriatric in-patients. *Drug Nutr. Interact.* **5**, 67-69.
- Ohta T, Maruyama T, Nagahashi M, Miyamoto Y, Yamazoe Y, Tsukamoto S, Paradisin C. (2002) a new CYP3A4 inhibitor from grapefruit juice. *Tetrahedron* **58**, 6631-6635.
- Page RL, Lawrence JD. (1999) Potentiation of warfarin by dong quai. *Pharmacotherapy* **19**, 870-876.
- Paolini M, Barillari J, Broccoli M, Pozzetti L, Perocco P, Cantelli-Forti G. (1999) Effect of liquorice and glycyrrhizin on rat liver carcinogen metabolising enzymes. *Cancer Lett.* **145**, 35-42.
- Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. (2002) The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin. Infect. Dis.* **34**, 234-238.
- Prost N, Tichadou L, Rodor F, Nguyen N, David JM, Jean-Pastor MJ. (2000) St Johns wort-venlafaxine interaction. *Presse Med.* **29**, 1285-1286.
- Rosado MF. (2003) Thrombosis of a prosthetic aortic valve disclosing a hazardous interaction between warfarin and a commercial ginseng product. *Cardiology* **99**, 111.
- Schelosky L, Raffauf C, Jendroska K, Poewe W. (1995) Kava and dopamine antagonism. *J. Neurol. Neurosurg. Psychiatr.* **58**, 639-640.
- Shannon M. (1997) Drug-drug interactions and the cytochrome P450 system: an update. *Pediatr. Emerg. Care* **13**, 350-353.
- Shannon M, Michael S. (2005) Drug-drug interactions. *Pediatr. Emerg. Care* **6**, 93-102.
- Sousa RL, Marletta MA. (1985) Inhibition of cytochrome P-450 activity in rat liver microsomes by the naturally occurring flavonoid, quercetin. *Arch. Biochem. Biophys.* **240**, 345-357.
- Sugimoto K, Ohmori M, Tsuruoka S, Nishiki K, Kawaguchi A, Harada K, Arakawa M, Sakamoto K, Masada M, Miyamori I, Fujimura A. (2001) Different effects of St John's wort on the pharmacokinetics of simvastatin and pravastatin. *Clin. Pharmacol. Ther.* **70**, 518-524.
- Sunter WH. (1991) Warfarin and garlic. *Pharm. J.* **246**, 772.
- Tannergren C, Engman H, Knutson L, Hedeland M, Bondesson U, Lennernas H. (2004) St John's wort decreases the bioavailability of R- and S-verapamil through induction of the first-pass metabolism. *Clin. Pharmacol. Ther.* **75**, 298-309.
- Taylor JR, Wilt VM (1999). Probable antagonism of

- warfarin by green tea. *Ann. Pharmacother.* **33**, 426-428.
- Westendorf J, Keller K, Hansel R, Chandler RF. Anthranoid derivatives-general discussion. In: De Smet PAGM. Adverse effects of herbal drugs, vol 2: 105.08.
- Yee GD, Stanley DL, Pessa L, Dalla Costa T, Beltz, SE, Ruiz J, Lowenthal DT. (1995) Effect of grapefruit juice on blood cyclosporin concentration, *Lancet* **345**, 955-956.
- Yu CM, Chan JC, Sanderson JE. (1997) Chinese herbs and warfarin potentiation by danshen. *J. Intern. Med.* **241**, 337-339.
- Yue QY, Jansson K. (2001) Herbal drug and anticoagulant effect with and without warfarin: possibly related to the vitamin E component. *J. Am. Geriatr. Soc.* **49**, 838.
- Zhou S, Lim LY, Chowbay B. (2004) Herbal modulation of P-glycoprotein. *Drug Metab. Rev.* **36**, 57-104.
- Zhou S, Chan E, Pan SQ, Huang M, Lee EJ. (2004) Pharmacokinetic interactions of drugs with St John's wort. *J. Psychopharmacol.* **18**, 262-276.