International Journal of Pharmaceutical Sciences and Nanotechnology

Volume 2 ● *Issue* 4 ● *January – March* 2010

Review Article

An Insight into Herb - Drug Interactions

Harish Chandra Rodda, Raj Kumar Molmoori, Sujatha Samala, Nagaraj Banala, Veeresham Ciddi*

University College of Pharmaceutical Sciences, Kakatiya University, Warangal - 506009, Andhra Pradesh, India

ABSTRACT: Alternative medicine is becoming popular worldwide and this is clearly evident from the rapidly escalating sales figures. The time tested and clinically proven herbal medicines like St. John's wort, *Ginkgo biloba*, Garlic, Ephedra, Echinacea etc., make up most of the world's market as for as alternative medicine is concerned. In spite of its increasing popularity, global criticism regarding the safety of herbal medicines is gaining importance. The surfacing of the adverse effects/adverse events due to concomitant use of herbs and prescription medicines undermine the safety of herbal medicines. The safety of herbal medicines still remains a daunting task. The herbs like St. John's wort, *Ginkgo biloba*, Garlic, Ephedra, Echinacea etc., have been reported to interact pharmacokinetically and pharmacodynamically with several prescription medicines. The available literature also bolsters that concomitant use of herbs and drugs can lead to several adverse effects/adverse events. This article presents most of the significant herb – drug interactions reported till date along with a note on the predicted interactions which may/may not occur. There are certain herb – drug combinations which can produce therapeutic benefit and these beneficial herb – drug combinations are also detailed in this article. This review gives an insight into herb – drug interactions, stressing the need to carryout studies on herb – drug interactions at a faster pace, which can strengthen the concept of herbal medicine.

KEYWORDS: Herbal medicine; herb – drug interactions; St. John's wort; CYP enzymes; predicted interactions; safe combinations

Introduction

Advances in western medicine have dramatically increased health conditions and life expectancy of people. In spite of the latest developments in allopathic system of medicine people still seek alternative and complimentary system. The use of herbal medicine to treat a wide range of conditions is rising rapidly, leading to increased intake of phytochemicals. Recent studies reveal potential fatal interactions between herbal medicines and drugs. Herbal medicine is amongst the 16 alternative systems of medicine, which is used to treat existing illnesses and also for preventive and health maintenance purposes (Ioannides, 2002). Herbs like St. John's wort, *Ginkgo biloba*, Feverfew, Ginger and Kava, Chamomile, Echinacea, Saw palmetto, Silymarin make most of the worlds market (Blumenthal, 1999). The increasing popularity of alternative therapies, including herbal remedies is a new challenge for health care providers because the evidence on safety of herbal remedies is incomplete, complex and confusing. The herbal medicines are certainly associated with risks and benefits (Ernst, 2003). Interactions between herbal medicines and drugs are based on the same pharmacokinetic and pharmacodynamic principles as drug – drug interactions. Clinically important interactions appear to involve effects on drug metabolism via cytochrome P-450 isoenzymes, impairment of hepatic or renal function, and other possible mechanisms (Dresser et al., 2000; Evans, 2000). The present review gives an insight into herb – drug interactions, clearly focusing the need to understand and also to assess the safety of herbal medicine. The content of the article is detailed from the therapeutic point of view of the herbs. Based on the possibility of co – administration herbs are classified into three categories i.e., category I – herbs having higher possibility of co – administration with drugs; category II – herbs having moderate possibility of co – administration with drugs and category III – herbs having less possibility of co – administration with drugs. This review also enlightens about the herbs which may/may not have inherent potential to interact with the drugs based on evidences of in – vitro studies, along with specific emphasis on the benefits of certain herb drug combinations.

* *For correspondence:* Veeresham Ciddi,

Tel.: 09849129584

E-mail: ciddiveeresham@yahoo.co.in

Interactions between Immunomodulatory Herbs – Drugs

The present day tech savvy world is beauty and health conscious and one of the popular uses of herbal medicine is to enhance immune system (Foti and Wholstrom, 2008). The global promotion of herbal products/herbal medicines as immune boosters is on the rise. Immunomodulation using herbs are always chosen as a better alternative to specific diseases, when the inherent defense of a person has to be activated under the conditions of impaired immune response (Atal et al., 1986). Ginseng is one of the highly commercialized immunomodulatory herbs, which is very common in most of the retail stores. Ginseng is purported to strengthen normal body functions increase resistance to stress and improve sexual function (Ellis and Reddy 2002). Ginseng is known to interact pharmacodynamically and pharmacokinetically with several drugs (Coon and Ernst 2002). Studies reveal that it alters the pharmacokinetics of the drugs like opioid analgesics (Abebe et al., 2002), bumetanide, ethacrynic acid, furosemide/torsemide, digoxin, amlodipine (Coon and Ernst, 2002). A pharmacodynamic interaction between *P. ginseng* and phenelzine is known to produce adverse effects like headache, tremulousness, manic episodes but the actual mechanism for this interaction is unknown (Jones and Runikis, 1987). Clinical studies on healthy volunteers reveal that ginseng and warfarin combination decreases the international normalized ratio (INR) values leading to increased risk of bleeding (Janetzky and Morreale, 1997) and it is bolstered by several studies(Jiang et al., 2004). Another immunomodulatory herb of choice is *Echinacea*, which is used as non-specific immunostimulant for upper respiratory tract infections. *Echinacea* is known to interact with drugs like itraconazle, fexofenadine and lovastatin (Budzinki, 2000). The active constituents of *Echinacea* are proven to be hepatotoxic and there is a possibility for potentiation of hepatotoxicity when it is co – administered with acetaminophen or other NSAIDs (Abebe et al., 2002). The immunomodulatory potential of *Echinacea* can lead to loss of activity of immunosuppressant drugs on concomitant usage (Daniel et al., 2006). The interaction potential of the other immunomodulatory herbs with the prescription drugs is listed in the Table 1.

Table 1. Interactions between Immunomodulatory herbs and drugs.

Herb	Drug/ Class of drugs	Possibility of co – administration	Mechanism/Outcome of Herb – Drug Interaction	Reference
Astragalus **(ASTRAGALUS MEMBRANACEUS)**	Azathioprine Cyclosporine Methotrexate	III	Antagonism	Zhou et al., 1982
Borage **(BORAGO OFFICINALIS)**	Hypnotics	II	Potentiation	Miller,1998
Echinacea **(ECHINACEA PURPUREA)**	Acetaminophen	II	Potentiation of Hepatotoxicity	Abebe et al., 2002
	Corticosteroids Cyclosporine	III	Antagonism	Miller,1998
	Fexofenadine Itraconazole Lovastatin	III	Inhibition of CYP3A4 leading to increase in drug concentration	Budzinki et al., 2000
Ginseng **(PANAX GINSENG)**	Amlodipine	I	Induction of CYP3A4	Dergal et al., 2002
	Digoxin	I	Increased drug concentrations	McRae et al., 1996; Dasgupta et al., 2003
	Hexobarbital	II	Induction of CYP2C9	Knodell et al., 1988
	Opioid analgesics	III	Decreased activity of opioids – clear mechanism is unknown	Takahashi and Tokuyama, 1998
	Phenelzine and MAO inhibitors	I	Increased CNS side effects due to additive effect	Jones et al., 1987
	Warfarin	II	Alteration of INR value	Cheng , 2000 Morreale, 1997 Jiang et al., 2004
Shankpushpi (**CONVOLVULUS PLURICAULIS**)	Phenytoin	I	Decreased therapeutic effect	Dandekar et al., 1992

I – herbs having higher possibility of co – administration with drugs; II – herbs having moderate possibility of co – administration with drugs; III – herbs having less possibility of co – administration with drugs

Interactions between Herbs used for Cardiovascular Disorders and Drugs

The herbal alternatives in cardiovascular risk group provide an additional benefit to the heart. It is with this credence that the herbs are used by cardiovascular risk group. It is revealed that 20% of the patients with acute coronary syndromes take herbal remedies for cardiac – specific purposes (Baracco et al., 2005). The herbs like *Allium sativum, Berberis aristata, Commiphora mukul, Rauwolfia serpentina, Stephania tetranda, Ligusticum wallichi, Uncaria rhyncophylla, Veratrum album, Cratageus monogyna, Allium sativum, Rosmarinus officinalis, Aesculus hippocastanum, Ruscus aculeatus* are widely used cardiovascular herbs (William et al., 2004). The herb – drug combinations in the cardiovascular risk group should be monitored very cautiously because failure to monitor such combinations can lead to life threatening events. Among these herbs garlic, guggul and hawthorn are reported to interact with drugs. The medicinal value of garlic has been accredited for more than 500 years. Garlic (*Allium sativum*) is used traditionally to treat infections, both orally and topically, promote wound healing and prevent cold and influenza (Harunobu et al., 2001). Modern use of garlic focuses on hyperlipidaemia, antihypertensive, antithrombotic and fibrinolytic effects, cancer prevention and antimicrobial effects (Stevinson et al., 2000; Ackermann et al., 2001). Till date the reports on herb – drug interactions with specific reference to garlic and drugs are very few. Garlic is reported to produce antihyperglycemic effect when it was co – administered with chlorpropamide (Aslam et al., 1979) and it also reported to alter the pharmacokinetics of saquinavir due to inhibition of P- glycoprotein (P – gP) (Piscitelli et al., 2002). Guggulipid, or gum guggulu, is an oleo gum resin extracted from the stem of the native Indian tree *Commiphora mukul*. Guggulipid has been in use traditionally as a treatment for obesity and associated lipid-related disorders, for arthritis and bronchitis, and topically for skin diseases (Mester et al., 1989). It may produce an additive effect with anticoagulants, and it is believed to act as a thyroid stimulating agent hence it is wise to avoid its co – administration with thyroid drugs because it may alter the dosage of thyroid medications[Tripathi et al., (1984); Panda and Kar (1999)]. In contrast to the above findings, guggul is predicted to decrease the absorption of beta blockers and calcium-channel blockers (Dalvi et al., 1994). This suggests that the dose adjustment of these drugs is required whenever they are co – administered with guggul.

Interactions between Herbs used for Central Nervous System Disorders and Drugs

The modern world is more prone to central nervous system (CNS) disorders. Statistics warn that the incidences of stress, depression, anxiety, mania and Alzheimer's disease are on alarming rise. According to the survey of Eisenberg et al., (1998) two of the top five conditions for which consumers choose alternative treatment are anxiety and depression. Depression and anxiety are prominent indications for herbal medicines (Roy-Byrne et al., 2005) and the majority of people with depression try complementary medicines (Silvers et al., 2006). A systematic review of the published literature reveal that *Ginkgo biloba, Lavandula angustifolia, Hypericum perforatum, Valeriana officinalis, Crataegus oxyacantha, Eschscholzia californica, Matricaria recutita, Melissa officinalis, Passiflora incarnata* and *Piper methysticum* are the commonly used herbs for CNS disorders. Among these, the use of herbal remedies like *Hypericum perforatum* (St John's wort) for mild to moderate depression, *Piper methysticum* (kava) for anxiety and *Ginkgo biloba* for cerebrovascuclar disorders are supported by sound evidences.

St.John's wort is a major herb of concern in herb – drug interactions due to its diverse pharmacological actions and unique potential to interact with vast majority of prescription drugs and OTC drugs like oral contraceptives. There are several studies, case reports and predictions about St. John's wort potential to alter the pharmacokinetics of drugs. It is reported to increase significantly the Cmax and AUC of the drugs such as fexofenadine, olanzapine and decrease the Cmax/AUC of the following drugs amitryptiline, midazolam, cyclosporine, digoxin, imatinib, irinotecan, indinavir, methadone, theophylline and oral contraceptives. The actual mechanisms and possibilities for the above mentioned St.John's wort mediated interactions are elaborated in Table 2. Of note, activation of CYP3A4 by St.John's wort interaction with oral contraceptives leading to failure of contraception, decrease in the AUC of tacrolimus and leading to increased risk of organ rejection are of primary significance (Bolley et al., 2002). An interesting study about St. John's wort reveals variation in the metabolism of drugs belonging to same class i.e., it decreases C_{max} and AUC of simvastatin but not pravastatin (Sugimoto et al., 2001). Similarly it is known to alter the pharmacokinetics of cyclosporine, an immunosuppressant (Barone et al., 2000) leading to graft rejection. In contrast to the above report it doesn't alter the pharmacokinetics of another immunosuppressant drug i.e., mycophenolate mofetil. This variation is attributed to involvement of hepatic enzymes in the metabolism of simvastatin and cyclosporine, while it is not so in case of pravastatin and mycophenolate mofetil

(Mai et al., 2003). From the above evidence it can be ear marked that mycophenolate can be good immunosuppressive drug of choice for those patients who are on treatment with St.John's wort. Pharmacodynamic interactions of St. John's wort with drugs are comparatively few when compared to pharmacokinetic interactions. Among the pharmacodynamic interactions it is observed that St.John's wort causes decreased myelosuppression incase of patients consuming irinotecan, increase in the viral load of patient consuming lamivudine and indinavir (due to increased CYP3A4 metabolism) were reported (Piscetilli et al., 2000). St.John's wort interaction with certain classes of drugs like serotonin selective reuptake inhibitors (SSRI) can lead to adverse effect like Serotonergic syndrome (Parker et al., 2001). St.John's wort and warfarin co – administration can lead to decreased INR leading to decreased anticoagulant activity which is strongly bolstered by 31 case reports. It is noteworthy that in spite of decrease in INR values, till date there are no reports of thromboembolic episodes in patients consuming St.John's wort and warfarin.

Ginkgo biloba is widely touted for its potential to ameliorate the cerebrovascular complications, dementia and for memory improvement (Kleijnen and Knipschild, 1992; Turan and Martorano 1995). *G. biloba* has special reference in herb - drug interactions because of the reported adverse events like intracerebral haemorrhage, subdural hematoma, and spontaneous hyphema. It is reported to interact prominently with blood thinning drugs (Chung et al.,1987) and this has been associated with the case reports postoperative bleeding (Fessenden et al., 2001), spontaneous hyphema (Rosenblat and Mindel, 1997), bilateral subdural hematomas (Rowin and Lewis., 1996). A single case report states that ginkgo increases the bioavailability of digoxin (Mauro et al., 2003) and other studies reveal that it decreases the bioavailability of omeprazole (Yib et al., 2004) and increases the bioavailability of diltiazem (Ohnishi et al., 2003). Pharmacodynamic alterations due to ginkgo and other drug combinations include decreased hypotensive effect of nicardipine (Shinozuka et al., 2002) and decreased antihyperglycemic effect of tolbutamide (Sugiyama et al., 2004).

Kava (*Piper methysticum*) is widely used herbal sedative (Keller and Klohs, 1963). The major active constituents of kava are kavalactones, which are potent inhibitors of CYP3A4 (Yadhu, 2005). Kava is reported to produce an additive effect in a 54yr old patient leading to semi comatose condition who was consuming alprazolam (CYP3A4 substrate) along with kava (Almeida and Grimsley, 1996). In contrast it is also reported that kava co – administration with bromazepam doesn't have any effect on the pharmacokinetics or pharmacodynamics of bromazepam (Heberg, 1996). A case report of severe Parkinsonism associated with kava and L – dopa co – administration contraindicates the combinative therapy (Schelosky et al., 1995).

Sarsaparilla is also used as an immunomodulator and to treat the respiratory disorders and also as an antidepressant (Chu et al., 2006; Spelmann et al., 2006). Theoretically sarsaparilla can potentiate the hypnotic activity of the concomitantly administered hypnotic drugs. Studies reveal that sarsaparilla can lead to increased drug activity of digoxin and bismuth because the saponins present in the herb enhance the absorption of drugs (Newall et al., 1996).

The interactions of other CNS herbs with various drugs are summarized in Table 2.

Interactions between Herbs and Drugs Acting On Blood (Blood Modifiers)

The use of traditional medicine in combination with alternative therapy may lead to complications for patients as it is evidenced by the adverse effects of certain herbal products in patients who receive traditional anticoagulant or antiplatelet medication. Most of the blood thinners are prescribed for patients who have heart valve replacement, atrial fibrillation, congestive heart failure, or for obese persons. They may also be used for the prevention of thromboembolic disorders (Gross and Weitz 2008). The long term and in certain cases life long use of blood thinning agents is imperative in cardiovascular risk patients. In these patients the use of certain herb – drug combinations should be avoided preferably due to the possibility for the risk of bleeding. Warfarin is the common drug which is reported to interact with several herbal formulations. The warfarin – herb interactions account to the extent of the 6 – 7 % of the interaction studies reported till date (Ann, 2001).The herbs/herbal formulations containing coumarins (arnica, celery, chlorella, danshen, dong quai, chamomile, fenugreek, goldenseal, guar gum, horse chestnut seeds, papain, passionflower, red clover, sweet clover, boldo) and vitamin K (acerola, agrimony , stinging nettle, plantain) as main active costituents alter the property of blood thinning drugs either by increasing or decreasing the bleeding phenomenon by altering international normalized ratio (INR). Certain herbs like bilberry, cayenne, bromelain, capsicum, European mistletoe, feverfew, garlic are known to reduce the platelet aggregation process and increase the fibrinolytic activity (Heck et al., 2000; Patel and Gohil, 2008). In contrast to the above, the herbs such as garlic, ginkgo and saw palmetto exceptionally inhibit platelet activating factor and this mechanism is considered to be the major perpetrator for the adverse events reported with the usage of these herbs (Rosenblatt and Mindel, 1997; Cheema et al., 2001).

Table 2. Interactions between herbs used for central nervous system disorders and drugs.

Herb	Herb Indication	Drug/Class of drugs	Possibility of co – administration*	Mechanism/Outcome of Herb Drug Interaction	Reference
Areca **(ARECA CATECHU)**	Antidepressant	Procyclidine	I	Antagonistic effect on ***drug – leading to extra pyramidal syndrome***	Deahl, 1989
Capsicum **(CAPSICUM FRUTESCENCE, CAPSICUM ANNUM)**	Circulatory stimulant, Pain reliever	ACE inhibitors	III	Increased risk of developing cough	Hakas, 1990
		Theophylline	II	Enhanced bioavailability can lead to theophylline toxicity	Bouraoui et al., 1988
Chasteberry **(VITEX AGNUS – CASTUS)**	Menopausal discomforts, inhibits secretion of prolactin	Dopamine receptor antagonists	III	Interferes with the activity of drugs	Meier et al., 2000
Feverfew (**TANACETUM PARTHENIUM**)	Arthritis, fever, Migraine headaches, digestive problems	Antimigraine Drugs	I	Potentiation of drug effect	Makheja et al., 1982
		Warfarin	II	Additive antiplatelet effect due to inhibition of platelet aggregation	Heck et al., 2000
Ginkgo **(GINKGO BILOBA)**	Improves memory, vasodilator	Aspirin Clopidogrel Ticlopidine	II	Increased risk of bleeding	Rosenblatt et al., 1997; Gianni, 1998
		Digoxin	II	Increased bioavailability of digoxin	Mauro et al., 2003
		Diltiazem	III	Increased bioavailability of drug	Ohnishi et al., 2003
		Ibuprofen	I	Intracerebral mass bleeding due to inhibition of platelet aggregation	Meisel et al., 2003
		Nicardipine	II	Induction of CYP 3A4 leading to decreased activity of drug	Shinozuka et al., 2002
		Phenytoin		Fatal seizures	Kupiec and Raj, 2005
		Omeprazole	III	Induction of CYP2C9	Yin et al., 2004
		Thiazide diuretics	III	Increase in blood pressure	Shaw et al., 1997
		Trazodone	II	Induction of CYP3A4	Dergal JM, et al., 2002 Galluzzi et al., 2000
		Warfarin	I	Increased risk of bleeding	Engelsen et al., 2003, Gianni and Dreitlein, 1998
Green tea **(CAMELIA SINENSIS)**	Cancer, heart problems, inhibits platelet aggregation	Warfarin	I	Increased risk of bleeding	Taylor et al., 1999

Guarana(**PAULLINIA CUPANA)**	Cognitive improver, antioxidant, antibacterial	Caffeine/ Respiratory stimulants	I	Potentiation of activity	Hess and Sullivan, 2005
Guggul	Lipid lowering activity	Diltiazem/Propranolol	I	Decreases the bioavailabilty of drugs	
Kava (**PIPER METHYSTICUM**)	Anxiolytic, antidepressant	Alprazolam	I	Potentiation of sedation	Almeida et al., 1996 Glesby, 1996
		Anesthetics	III	Prolongation of anesthesia	Raduege et al., 2004
		Levodopa	I	Antagonism	Schlelosky et al., 1995
Lemon balm **(MELISSA OFFICINALIS)**	Depression, nervous insomnia, antioxidant	CNS depressants	II	Additive CNS effects	Wong et al., 1998
		Thyroid hormones	III	Inhibits binding of thyroid hormones to TSH receptors	
Sage **(SALVIA MITILIORRHIZA)**	Insomnia, Blood purifier	Warfarin	I	Increased risk of bleeding	Tam et al., 1995, Chan, 1998
		Diazepam	I	Induction of enzymes	Jinping et al., 2003
St.John's wort **(HYPERICUM PERFORATUM)**	Antidepressant and antiviral	Amitryptyline	II	Induction of CYP3A4	Johne et al., 2002
		Cyclosporine	III	Induction of CYP3A4 and P - gP leading to decrease in drug concentration and rejection of transplanted organ	Mai et al., 2000; Ruschitzca et al., 2000; Barone et al., 2000
		Digoxin	III	Induction of P – gP	Mueller et al., 2004; Johne et al., 1999
		Fexofenadine	III	Inhibition of P - gP	Wang et al., 2002
		Indinavir, Saquinavir	II	Induction of CYP 3A4	Piscitelli et al., 2000 Piscitelli et al., 2002
		Irinotecan	I	Decreased concentration of drug	Mathijssen et al., 2002
		Loperamide	III	Acute delirium – mechanism unknown	Khawaja et al., 1999
		Methadone	II	Induction of CYP 3A4, 2C8 and CYP 2D6 leading to decrease in drug concentration	Eich – Hochli, et al., 2003
		Oral Contraceptives	II	Failure of contraception due to induction of CYP3A4	Hall et al., 2003; Pfrunder et al., 2003; Schwarz, 2003; Hindmarch, 2002
		Piroxicam Photosensitizing drugs	III	Increased risk of phototoxicity	Miller, 2001

		Quazepam	III	Induction of CYP 3A4	Kawaguchi et al., 2004
		Sertraline	I	Inhibits vesicular uptake of monoamines leading to serotonergic syndrome	Roz et al., 2002
		Simvastatin	I	Induction of CYP3A4	Sugimoto et al., 2001
		Tacrolimus	II	Immuno graft rejection due to induction of CYP enzymes	Mai et al., 2003 Hebert et al., 2004
		Theophylline	II	Induction of CYP1A2 leading to decreased concentration of drug	Nebel et al., 1999 Morimoto et al., 2004
		Thyroid stimulating hormone	III	Elevation of TSH levels	Ferko and Levine, 2001
		Venlaxafine	I	Serotonin syndrome – Inhibition of serotonin reuptake and MAO Inhibition	Prost et al., 2000
		Verapamil	III	Induction of CYP3A4, leading to decreased bioavailabilty	Tannergren et al., 2004
		Warfarin	II	Induction of CYP3A4 and CYP2C9	Jiang et al., 2004
Valerian **(VALERIANA OFFICINALIS)**	Muscle relaxant, insomnia, GIT pains	Barbiturates	I	Additive sedation	Willey, 1995
		haloperidol	I	Inhibition of delta – ALA – D activity	Dalla et al., 2008
Yohimbine (**PAUSINYSTALIA YOHIMBE**)	Antidepressant, erectilfe dysfunction	Clomipramine	I	Increased blood pressure	Lacombiez et al., 1989

* I – herbs having higher possibility of co – administration with drugs; II – herbs having moderate possibility of co – administration with drugs; III – herbs having less possibility of co – administration with drugs

Interactions between Other Herbs and Drugs

Artemesinin

Artemisinin, an antimalarial herb is reported to induce its own elimination and that of omeprazole through an increase in CYP2C19 activity (Svensson et al., 1998).

Foeniculum vulgare

The antidiabetic herb *Foeniculum vulgare* has been reported to decrease the rate of absorption of ciprofloxacin due to chelation of the drug by the metal ions present in the plant extract (Zhu et al., 1999).

Liquorice

Liquorice is used as a natural sweetening agent and also for treatment of gastric ulcers. It can interact with antihypertensive drugs leading to synergistic effect (Cumming et al., 2003); hydrocortisone leading to pseudoaldosteronism (Beate et al., 1999); oral contraceptives leading to hypertension, edema and hyperkalemia (Gerty et al., 1997).

Silymarin

Silymarin is being used for more than 2000 years to treat liver, gall bladder disorders, including hepatitis, cirrhosis, and jaundice and to protect liver against poisons from chemical and environmental toxins (Vladimir and Daniela, 2005). Silymarin is reported to potentiate the effects of antiarrhythmic drugs (Gyonos et al., 2001), increase the pharmacological activity of cisplatin (Scambia et al., 1996), decrease the blood concentrations of indinavir (Piscitelli et al., 2002), losartan (Han et al., 2009) and metronidazole(Chon et al, 2005).

Herbs used by women

Women periodically experience changes with menstrual regularity, an absence of a menstrual cycle (amenorrhea), premenstrual tension, bloating, cramping and mood fluctuations (dysmenorrhea), flooding and heavy cycles (menorrhagia), fluid retention, irritability, migraines, skin problems, irregular or heavy menses, pelvic congestion, fibroids, endometriosis and cysts. Herbal medicines provide gentle support to women by nourishing reproductive tissues and regulating hormones secreted by the pituitary and adrenal glands. These hormones influence ovarian function, regulate menstrual flow, minimize cramping and stabilize mood changes. Herbs are also used by women to support liver function, which facilitate in breaking down excess circulating hormones, to accelerate their removal from the body, to minimize fluid retention and to provide direct antispasmodic action for pain management and cramping. The herbs like False Unicorn (*Chamaelirium luteum*), Partridge Berry (*Mitchella repens*), Chaste berry (*Vitex agnus castus*), Motherwort (*Leonurus cardiaca*), Red Raspberry (*Rubus idaeus*) are used as reproductive tonics. Herbs like Dong Quai (*Angelica sinensis*), Black cohosh (*Cimicifuga racemosa*), Mugwort (*Artemisia vulgaris*), Rue (*Ruta graveolens*) are used as emmenagogues, which stimulate, regulate and promote a normal menstrual flow. The herbs like Shepherds Purse (*Capsella bursa pastoris*), Cayenne (*Capsicum minimum*), Lady's Mantle (*Alchemilla vulgaris*), Beth Root (*Trillium erectum*) are used as astringents which reduce the menstrual flow and excessive bleeding by contracting blood vessels and tightening mucous membranes. The herbs like Dandelion Leaf (*Taraxacum officinalis*), Yarrow (*Achillea millefolium*), Cleavers (*Galium aperine*) are used to reduce or eliminate fluid retention associated with premenstrual tension by increasing the flow of urine. Chamomile, Dandelion and Dong quai are the herbs widely used by women which have interaction potential with the drugs. Studies reveal chamomile administration with opioids leads to increased CNS depression (Abebe et al., 2002), dandelion if co –administered with diuretic drugs can potentiate the diuretic effect (Akthar et al., 1985), Dong quai (*Angelica dahurica*) is reported to increase the C_{max} and AUC of diazepam along with an increase in $t_{1/2}$ of tolbutamide (Ishihara et al., 2000).

Weight loss supplements

The weight loss supplements like ephedra and germander have interaction potential with drugs. Ephedra can increase the risk of gastric lesions when co-administered with loxoprofen (Cho et al., 2002). It is evident from clinical reports that ephedra can increase the risk of seizures when co – administered with anticonvulsants (Spinella, 2001). Germander, another weight loss supplement can lead to liver damage when co – administered with dexfenfluramine (Mostefa et al., 2000).

Herbs Proven to Alter Cytochrome P450 Enzymes in *In - Vitro* Models

Cytochrome P450 (CYP) enzymes are involved in the metabolism of a multitude of drugs. These enzymes are involved in numerous interactions between drugs and food, herbs and other drugs. The observed induction and inhibition of CYP enzymes by natural products in the presence of a prescribed drug can result in adverse effects. *In vitro* studies reveal that herbal medicines and their biomarkers have potential to modulate the - CYP enzymes. These evidences need support in the form of systematic studies, so that metabolism – based interactions can be predicted and avoided more readily in clinical applications or by health care professionals (Delgoda and Westlake 2004). The potential of herbs to induce/inhibit the CYP enzymes in various *in vitro* models are summarized in Table 3.

Table 3. Herbs proven to alter cytochrome P450 enzymes in in - vitro models.

Herb	Herb Indication	CYP Enzyme	In – vitro model	Reference
ANGELICA DAHURICA	Analgesic, Diuretic, Antibacterial	Inhibits CYP3A4	Inhibtis multidrug-resistant and methicillin-resistant strains of *Staphylococcus aureus* Liver microsomes	Lechner et al., 2004, Guo et al., 2001
Devil's Claw (**HARPOGOPHYTUM PROCUMBENS**)	Arthritis,sedative	CYP2C8,CYP2C19, CYP3A4,CYP1A2, CYP2D6	Human kidney (HK-2) proximal tubule cell line	Nadia et al., 2009
Echinacea (**ECHINACEA PURPUREA**)	Immunomodulator	Inhibits CYP2C19, CYP2D6	Baculovirus expressed CYP enzymes	Modarai et al., 2007
Garlic (**ALLIUM SATIVUM**)	Reduces cholesterol levels	Inhibits CYP2C9, CYP2C19, Inhibits CYP3A4 Inhibits CYP2E1	Human liver microsomes CYP 3A4 Substrates (7-Benzyloxyresorufin and 7-ethoxy-3 cyanocoumarin Rat iver microsomal cytochrome P450 fractions	Greenbalt et al., 2006 Foster et al., 2001 Caro and Cederbaum, 2005
Ginseng (**PANAX GINSENG**)	Immunomodulator	Inhibits CYP1A2, CYP2B1, CYP2C9,CYP3A4	c-DNA-expressed cytochrome P450 enzyme catalytic activity	Henderson et al., 1999
Goldenseal (**HYDRASTIS CANADENSIS**)		CYP2D6, CYP3A4, CYP3A5	Caco – 2 cell lines	Chatterjee and Franklin, 2003
Kava (**PIPER METHYSTICUM**)	Anxiety, depression	Inhibits CYP3A4, CYP1A2, CYP2C9, CYP2C19,CYP2D6	Human liver microsomes	Mathews et al., 2002 Mathews et al., 2005
Liquorice (**GLYCYRRHIZA GLABRA**)	Expectorant, antioxidant, allergic inflammation	CYP3A4, CYP2C9	Human recombinant enzymes	Kent et al., 2002 Sachiko et al., 2005
Saw palmetto (**SERENOA REPENS**)	Benign Prostatic Hyperplasia	Inhibits CYP3A4, CYP2C9 and CYP2D6	Healthy volunteers	Yale and Glurich, 2005
Schizandra (**SCHIZANDRA CHINENSIS**)	Sedative, Diuretic	Inhibits CYP3A4	Liver microsomes	Iwata et al., 2004
Silymarin (**SILYBUM MARIANUM**)	Hepatoprotective	Inhibits CYP3A4 CYP2C9	Human hepatocytes/ Human recombinant enzymes	Venkataramanan et al., 2000
Valerian (**VALERIANA OFFICINALIS**	Insomnia, Muscle relaxant	Inhibits CYP3A4, CYP2C9 and CYP2C19	Cytochrome P450 CYP3A4 supersomes	Tania et al., 2004
Vinca **(CATHARANTHUS ROSEUS)**	Anticancer	Inhibits CYP2D6	Human Liver Microsomes	Usia et al., 2005

* I – herbs having higher possibility of co – administration with drugs; II – herbs having moderate possibility of co – administration with drugs; III – herbs having less possibility of co – administration with drugs

Predicted Herb - Drug Interactions

Perusal of available literature reveals many theoretical herb - drug interactions, which are based on assumptions and which lack sound scientific evidences. These interactions are based on activity of constituents contained in herbs or herbs having similar pharmacological potential as that of the drugs or herbs having toxic potential similar to drugs. These theoretical considerations may/may not confer that they will produce an interaction in – vivo.

Laxative herbs like senna, aloe, cascara etc increase motility of gastrointestinal tract and hence they may increase the elimination rate of drugs. Senna, widely used herbal laxative is known to decrease the serum concentration of digitalis (Botzler, 1982). Herbs can also alter the absorption of drugs. It is believed that absorption of iron formulations can be inhibited by saw palmetto (*Serenoa repens*) and the saponins present in the sarsaparilla (*Smilax ornata*) plant can increase the absorption digitalis and bismuth which can lead to toxic symptoms.

The herbs and drugs having similar pharmacological profile when co - administered can lead to potentiation of pharmacological effect. If sedative herbal medicines like hops (*Humulus lupulus*), kava (*Piper methysticum),* valerian (*Valeriana officcinalis*), bupleurum (*Bupleureum falcatum*) are co – administered with the sedative/anxiolytic drugs then there is a possibility for potentiation of sedative effect. A case report leading to semi - comatose condition in a 54 yr old patient has been documented who was concomitantly using kava and alprazolam (Almeida and Grimsley 1996). This case report suggests that it is sensible to avoid the use of sedative herbs like hops, chamomile, kava and valerian along with the sedative drugs. Similarly the herbs having central nervous stimulatory effect can lead to enhanced stimulation of nervous system if co –administered with the central nervous system stimulant(CNS) drugs. Theoretically, co – administration of kola – nut along with theophylline can lead to potentiation of CNS effects. In similar lines herbs used as diuretics should not be concomitantly used with diuretic drugs.As a general concept it is preferable to avoid the combinative usage of the herbs and drugs having similar toxic potential. Most of the available literature cautions that there is greater chance for potentiation of hepatotoxicity when hepatotoxic herbs like chapparal (*Larrea tridentata*), germander (*Teucrium chamaedrys*), echinacea (*Echinacea purpurea*) are co – administered with hepatotoxic drugs such as non steroidal anti – inflammatory drugs (NSAIDs), ketoconazole and methotrexate.

Herb – drug combinations can also lead to antagonism of drug activity if they have opposing mechanism of actions. It is speculated that the activity of dopamine containing drugs may be antagonized by the kava due to its dopamine antagonistic properties.

Herbs altering the electrolyte balance in the body can alter the pharmacokinetics/pharmacodynamics of drugs which mediate their actions through the ionic mechanisms. The herbs such as liquorice and herbal laxatives alter the ionic concentrations in the body can lead to alteration in the activity of drugs like digitalis, antihypertensive and diuretic drugs.

Herbs have potential to alter the intraoperative complications and also postoperative complications (Ang-Lee et al., 2001; Deron and Deborah 2003). These herbs may alter the effects of anesthesia or may alter the kinetics/dynamics of postoperative medications. This interaction of potential of herbs with anesthetics and postoperative medications stresses the need to avoid usage of herbal medicines, well in advance before any surgical intervention. In certain cases herbs have potential to enhance the intraoperative bleeding. A case report of severe intraoperative bleeding has been reported in a patient consuming Saw palmetto (Cheema et al., 2001). Another case report of cardiovascular collapse has been reported in a patient during induction of anesthesia and the possible mechanism has been attributed to long term consumption of St.John's wort (Samuel and Juraj, 2000) Herbs can lead to alteration in the postoperative conditions resulting either in enhanced hypotension or prolongation of anesthetic effect. Capsicum has potential to increase risk of bleeding, allergic reactions, decrease the effectiveness of immunosuppressants and it can produce immunosuppresion on long-term usage. Ephedra is known to have risk of myocardial ischemia, tachycardia, hypertension and it may also produce ventricular arrhythmias when combined with anesthetics (Kaye et al., 2000; Renfrew et al 2000). Long-term use of ephedra is known to deplete the endogenous catecholamines which can cause intraoperative hemodynamic instability and life-threatening interaction with monoamine oxidase inhibitors (Ling et al., 1995). Hence anesthetists specify discontinuation of ephedra usage at least 24 hours prior to any surgical intervention. Feverfew, garlic, ginger and ginkgo have potential to increase the risk of bleeding due to their platelet inhibition potential (German et al., 1995; Norred and Finlayson, 2000). A case report of post operative bleeding had been reported with the use of ginkgo biloba in a liver transplant patient (Hauser et al., 2002). Hence it is safe to discontinue the usage of these herbs 1 week before surgery and use of ginkgo at least 36 hours before surgery. Ginseng can produce hypoglycemia,

can increase the risk of bleeding and it also has potential to decrease anticoagulation effect of warfarin therefore usage should be avoided at least 1 week prior to surgerical intervention (Norred and Finlayson, 2000). St.John's wort may prolong effects of anesthesia and it has potential to induce cytochrome P450 enzymes, which may affect the kinetics of several classes of drugs. It is prudent to avoid usage of St. John's wort at least 5 days before any surgical intervention. Kava and valerian may increase sedative effect of anesthetics and kava usage should be avoided at least 1 day before surgical procedure (Saba et al., 2001). It is reported that Dong quai (*Angelica sinensis*) is the cause of hypertension in a 32-year-old woman with 3 weeks post-partum (Nambiar et al., 1999). The platelet inhibitory potential of Aloe vera is reported to be the cause of massive intraoperative bleeding in a 35 yr old woman who was consuming *Aloe vera* tablets (Lee et al., 2004). Goldenseal (*Hydrastis canadensis*) can worsen edema or hypertension, liquorice may cause high blood pressure, swelling or electrolyte imbalance, hence it's wise to avoid the use of this herb prior to surgery because the post and preoperative data are not available for this herb (Deron and Deborah, 2003).

The other Side of Herb – Drug Interactions

Along with an exhaustive list of herb – drug interactions which need special precautions there are some herb - drug combinations which are quite safe. In some cases, herbs have been shown to mitigate or prevent adverse effects associated with drugs. For example, aromatic herbs such as ginger can be used to prevent drug-induced nausea; milk thistle can be used to prevent the liver toxicity associated with drugs. In addition, the scientific studies have proven that capsaicin reduces gastric mucosal damage induced by aspirin (Yeoh et al., 1995) and St. John's wort doesn't interact with carbamazepine, pravastatin, mycophenolate mofetil (Sugimoto et al., 2001; Bolley et al., 2002Mai et al., 2003). Hawthorn is useful for angina and it is as an alternative to digitalis in Europe. A study on digoxin and hawthorn revealed that their combined use has no significant interaction and they can be used safely (Tankanow et al., 2003). Animal studies have shown that the combination of aqueous extract of Chinese medicinal plant *Tripterygium wilfordi* and cyclosporine significantly increases the heart and kidney allograft survival compared to cyclosporine alone (Wang et al., 2000). It is also proven that garlic prevents the formation of toxic metabolites of paracetamol, co – administration of ginkgo with antipsychotics (haloperidol) in chronic schizophrenic patients reduces extra pyramidal side effects associated with haloperidol (Sasaki et al., 2000; Zhang et al., 2001). *Centella asiatica* can also be used as an adjunctive medication for patients with epilepsy due to its additive anticonvulsant activity (Vattanajun et al., 2005). *Momordica charantia* is reported to augment the hypoglycemic effect of rosiglitazone which can be used to reduce the dose of rosiglitazone to achieve enhance therapeutic effect with minimum side effects (Susan et al., 2009). Piperine can be used as bioavailability enhancer for several drugs and studies bolster that piperine enhances the bioavailability of propranolol which can be used as a means to achieve better therapeutic control and improved patience compliance (Bano et al., 1991). In the similar lines Ginseng is considered to be potent adjuvant for delivery of vaccines which have been proven to induce higher or similar antibody titres than vaccines adjuvanted with aluminium hydroxide (Rivera et al., 2003). Further, studies also prove that Rosemary (*Rosmarinus officinalis*) has chemopreventive effect as it increases efflux and intracellular accumulation of doxorubicin and vinblastine (Huang et al., 1994). In vitro studies also revealed that silybinin enhances the antitumour activity of cisplatin (Scambia et al., 1996). All these data suggest that synergistic potential between herbal medicines and drugs can be therapeutically advantageous, clearly stressing the need for extensive work to be done in this area.

Conclusion

People use herbal medicines so as to ensure general health and nutrition. The magnitude of herb – drug interactions are less common when compared to drug – drug interactions. Recent estimates also specify that drug – drug interactions are considered to be the fourth leading cause of death in hospitalized patients. In spite of the vast majority of drug – drug interactions which are documented most commonly, the downplaying attitude of allopathic physicians elevates the concern on herb – drug interactions which occur very rarely. Till date the interactions of St.John's wort, ginkgo, ginseng, garlic and ephedra with drugs are of major concern because of the magnitude of evidences available. A close look into the herb – drug interactions reveal that most of them are based on excess consumption of herbs, irrational use in geriatric patients, a few case reports on patients/healthy volunteers and few scientific studies conducted in animals. Many of the herb – drug interactions die unnoticed by the physicians until an adverse effect or adverse event occurs. In comparison with the drug – drug interactions the extent of herb – drug interactions is not alarming but there is a great concern about safety of herbal medicine. In spite of the entire herb - drug interactions listed there are certain herb – drug combinations which are safe, certain combinations which increase the bioavailability of drugs, prevent formation of

toxic metabolites of drugs, which can be used as adjuvants to deliver vaccines. In view of this, there is an urgent need to critically evaluate herb – drug interactions along with an equal responsibility on healthcare professionals to highlight the safe herb – drug combinations and to establish the safety of herbal medicine. The new evidences in support of herb – drug interactions will dispel the fears about usage of certain herb - drug combinations, can guide to monitor the therapeutic regimens of drugs and to avoid concomitant use of herbs and drugs which are harmful.

References

Abebe W. Herbal Medication: potential for adverse interactions with analgesic drugs. *J. Clin. Pharm. Ther*. **27:** 391-401 (2002).

Ackermann RT, Mulrow CD, Ramirez G, Gardner CD, Morbidoni L and Lawrence VA. Garlic shows promise for improving some cardiovascular riskfactors. *Arch. Intern. Med*. **161**: 813-824 (2001).

Akhtar MS, Khan QM, and Khaliq T. Effects of *Portulacca oleracae* (Kulfa) and *Taraxacum officinale* (Dhudhal) in normoglycaemic and alloxan-treated hyperglycaemic rabbits. *J. Pak. Med. Assoc*. **35:** 207-210 (1985).

Almeida JC and Grimsley EW. Coma from health food store: interaction between kava and alprazolam. *Ann. Intern. Med.* **125:** 940-941 (1996).

Ang-Lee MK, Moss J, Yuan CS.Herbal Medicines and Perioperative Care. *J. Am. Med. Assoc*. **286:** 208-216(2001).

Ann KW. Drug interactions update: Drugs, Herbs and oral anticoagulation. *J. Thromb. Thromoboly*. **12:** 67-71 (2001).

Arterioscl. Thromb. Vasc. Biol. **28:** 380-386 (2008).

Aslam M and Stockley IH. Interaction between curry ingredient (karela) and drug (chlorpropamide). *Lancet*. **1:** 607 (1979).

Atal CK, Sharma ML, Kaul A and Khajuria A. Immunomodulating agents of plant origin I: Preliminary screening. *J. Ethnopharmacol*. **18:** 133-141(1986).

Bano G, Raina RK, Zutshi U, Bedi KL, Johri RK and Sharma SC. Effect of piperine on bioavailability and pharmacokinetics of propranolol and theophylline in healthy volunteers. *Eur. J. Clin. Pharmacol.* **41:** 615-617(1991).

Baracco D, Valenica G, Riba AL, Nareddy S, Draus CB and Schwartz SM. Complementary and alternative medicine(CAM) use patterns and disclosure to physicians in acute coronary syndrome patients. *Complement. Ther. Med*. **13:** 34 -40 (2005).

Barone GW; Gurley BJ, Ketel BL, Lightfoot ML and Abul-Ezz SR. Drug interaction between St. John's wort and cyclosporin. *Ann. Pharmcother*. **34:** 1013-1016 (2000).

Beate MD and Andler W. Liquorice, Growth Retardation and Addison's disease. *Horm. Res.* **52:** 253-255 (1999).

Blumenthal M. Herbal market levels afer five years of boom. *Herb. gram*. **47:** 64-65 (1999).

Bolley R, Zulke C, Kammerl M, Fischereder M and Kramer BK. Tacrolimus – induced nephrotoxicity unmasked by induction of CYP3A4 system with St. John's wort. *Transplantation*. **73:** 1009 (2002).

Botzler R and Ritter U. Effect of laxative measures on the serum concentration of digoxin in the human. *Leber. Magen. Darm*. **14:** 255-257 (1982).

Bouraoui A, Toumi A, Ben Mustapha H and Brazier JL. Effects of capsicum fruit on theophylline absorption and bioavailability in rabbits. *Drug. Nutrient. Interact*. **5:**345-350 (1988).

Brian CF, Meredith SF, Susan V, Anthony K, Keith DG, and Shurjeel C. An in vitro evaluation of human cytochrome P-450 and P- glycoprotein inhibition by garlic. *J. Pharmaceut. Sci.* **4:** 176-184 (2001).

Budzinski JW, Foster BC, Vandenhoek S, and Arnason JT. An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. *Phytomed*. **7:** 273-282 (2000).

Caro AA and Cederbaum AI. Inhibition of CYP2E1 catalytic activity in vitro by *S*-adenosyl-l-methionine. *Biochem. Pharmacol*. **69:** 1081-1093 (2005).

Chan TYK. Drug interactions as a cause of over anticoagulation and bleedings in Chinese patients receiving warfarin. *Int. J. Clin. Pharmcol. Ther*. **36:** 403-405 (1998).

Chang Q, Zuo Z, Harrison F and Chow MS. Hawthorn. *J. Clin. Pharmacol*. **42:** 605 (2002).

Chatterjee P, and Franklin MR. Human cytochrome P-450 inhibition and metabolic-intermediate complex formation by goldenseal extract and its methylenedioxyphenyl components. *Drug. Metab. Dispos*. **31**: 1391-1397 (2003).

Cheema P, El – Mefty O and Jazieh AR. Intraoperative hermorrhage associated with the use of extract of Saw Palmetto herb; A case report and a review of literature. *J. Int. Med*. **250:** 167-169 (2001).

Cheng TO. Ginseng–warfarin interaction. *ACC. Curr. J. Rev*. **9:** 84 (2000).

Cho S, Hong T, Jin GB, Yoshino G, Miura M, Aikawa Y, Yasuno F and Cyong JC. The combination therapy of Ephedra herb and Loxoprofen caused gastric lesions in mice. *Am. J. Chin. Med*. **30:** 571-577 (2002).

Chon SK and Kim NS. Evaluation of silymarin in the treatment on asymptomatic Giardia infections in dogs. *Parasitol. Res.* **97:** 445-451(2005).

Chung KF, Dent G, McCuster M, Guinot P, Page CP and Barnes PJ. Effect of ginkgolide mixture (BN 52063) in antagonizing skin and platelet responses to platelet activating factor in man. *Lancet*. **1:**248-251(1987).

Coon JT and Ernst E. *Panax ginseng*: a systematic review of adverse effects and drug interactions. *Drug Safety*. **25:** 323-344 (2002).

Dalvi SS, Nayak VK, Pohujani SM, Desai NK, Kshirsagar NA and Gupta KC. Effect of gugulipid on bioavailability of diltiazem and propranolol. *J. Assoc. Physci. India.* **42:** 454-455 (1994).

Dandekar UP, Chandra RS, Dalvi SS, Joshi MV, Gokhale PC, Sharma AV, Shah PU and Kshirsagar NA. Analysis of a clinically important interaction between phenytoin and shankpushpi an Ayurvedic preparation. *J. Ethnopharmacol.* **35:** 285-288 (1992).

Daniel P, Jean J D, Edward M, and Gideon K. Safety and efficacy of Echinacea (*Echinacea angustifolia, E.purpurea and E. pallida*) during pregnancy and lactation. *Can. J. Clin. Pharmacol* . **13:** 262-267 (2006).

Dasgupta A, Wu S, Actor JK, Olsen M, Wells A and Datta P. Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays: significant variation in digoxin-like immunoreactivity among commercial ginsengs. *Am. J. Clin. Pathol*. **119:** 298-303 (2003).

David JG, Richard A, Leigh P, Lisa L, and Moltke V. In Vitro Interactions of Water-Soluble Garlic Components with Human Cytochromes P-450. *Biochem. Pharmacol.* **69:** 1081-1093 (2005).

Deahl M. Betel nut-induced extrapyramidal syndrome: an unusual drug interaction. *Mov. Disord*. **4:** 330–333(1989).

Delgoda R and Westlake ACG. Herbal Interactions Involving Cytochrome P-450 Enzymes: A Mini Review. *Toxicol. Rev*. **23:** 239-249 (2004).

Deron JT and Deborah SB. A surgeon's guide to herbal supplements. *J. Surg. Res.***114**: 30-36 (2003).

Dresser GK, Spence JD, and Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P-4503A4 inhibition. *Clin. Pharmacokinet*. **38:** 41-57 (2000).

Eich-Hochli D, Oppliger R, Golay KP, Baumann P and Eap CB. Methadone maintenance treatment and St. John's wort: a case report. *Pharmacopsych*. **36**: 35-37 (2003).

Ellis JM and Reddy P**.** Effects of *Panax ginseng* on quality of life. *Ann. Pharmacother*. **36:** 375-379 (2002).

Engelsen J, Nielsen JD, and 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. Laegr*. **165:** 1868-1871 (2003).

Ernst E. Herbal Medicines put into context. *Br. Med. J*. **327:** 881-882 (2003).

Ferko N and Levine MA. Evaluation of the association between St.John's wort and elevated thyroid –stimulating hormone. *Pharmacother*. **21**: 1574-1578 (2001).

Fessenden JM, Wittenborn W, and Clarke L. Ginkgo biloba: a case report of herbal medicine bleeding postoperatively from a laparoscopic cholecystectomy. *Ann. Surg.* **67:** 33-35 (2001).

Foti S and Wholstrom JL. The role of dietary supplements in cytochrome P450 – mediated drug interactions. *Bol. Latinoam. Caribe. Plant. Med. Aromaticas*. **7:** 66-84 (2008)

Galluzzi S, Zanetti G, Trabucchi M and Frisoni GB. Coma in patient with Alzheimer's disease taking low dose trazodone and *Ginkgo biloba*. *J. Neurol. Neuosurg. Psychiatr*. **68:** 679-680 (2000).

German K, Kumar U and Blackford HN. Garlic and the risk of TURP bleeding. *Br. J. Urol.* **76:** 518 (1995).

Gerty JK, Marietje GN**,** and Jaap JB**.** Lesson of the week: hypokalaemia and hypertension associated with use of liquorice flavored chewing gum. *Br. Med. J*. **314:** 731 (1997).

Gianni L and Dreitlein WB. Some popular OTC herbals can interact with anticoagulant therapy. *US Pharm.* **23:** 80 (1998).

Glesby MJ and Hoover DR. Coma from health food store: interaction between kava and alprazolam. *Ann. Intern. Med*. **125:** 940-941 (1996).

Gross PL, and Weitz JI. New Anticoagulants for treatment of venous thromboembolism.

Guo LQ, Taniguchi M, Chen QY, Baba K and Yamazoe Y. Inhibitory potential of herbal medicines on human cytochrome P-450 mediated oxidation; properties of umbelliferous or citrus crude drugs and their relative prescriptions. *Jpn. J. Pharmacol*. **85**: 399-408 (2001).

Gyonos I, Agoston M, Kovacs A, Szenasi G and Vereckei A. Silymarin and vitamin E do not attenuate and vitamin E might even enhance the antiarrhythmic activity of amiodarone in rat reperfusion arrhythmia model. *Cardiovasc. Drugs. Ther*. **15:** 233-240 (2001).

Hakas JFJ. Topical capsaicin induces cough in patient receiving ACE inhibitor. *Ann. Allergy*. **65:** 322-323 (1990).

Hall SD, Wang Z, Hunag SM, Hamman MA, Vasavada N, Adigun AQ, Hilligos JK, Miller M and Gorski JC. The interaction between St. John's wort and oral contraceptives. *Clin. Pharmacol. Ther*. **74:** 525-535 (2003).

Han Y, Guo D, Chen Y, Chen Y, Tan ZR, and Zhou HH. Effect of silymarin on the pharmacokinetics of losartan and its active metabolite E-3174 in healthy Chinese volunteers. *Eur. J. Clin. Pharmacol.* **65:** 585-91 (2009).

Harunobu A, Brenda IP, Hiromichi M, Shigeo K and Yoichi I. Recent advances on the nutritional effects associated with the use of garlic and its bioactive components. *J. Nutr*. **131:** 955-962 (2001).

Hauser D, Gayowski T, and Singh N. Bleeding complications precipitated by unrecognized *Ginkgo biloba* use after liver transplantation. *Transpl. Int*. **15:** 377-379 (2002).

Hebert MF, Park JM, Chen YL, Akthar S and Larson AM. Effects of St.John's wort (*Hypericum perforatum*) on tacrolimus pharmacokinetics in healthy volunteers. *J. Clin. Pharmacol.* **44:** 89-94 (2004).

Heck AM, DeWitt BA and Lukes AL. Potential interactions between alternative therapies and Warfarin. *Am. J. Health. Syst. Pharm*. **57:** 1221-1227 (2000).

Henderson GL, Harkey MR, Gershwin ME, Hackman RM, Stern JS and Stresser DM. Effects of ginseng components on c-DNA-expressed cytochrome P-450 enzyme catalytic activity. *Life Sci*. **65:** 209-214 (1999).

Herberg KW. Safety – related performance after intake of kava and their combination. *Z. Allegeinmed.* **72:** 973-977 (1996).

Hess AM and Sullivan DL. Potential toxicity with use of bitter orange extract and guarana for weight loss. *Ann. Pharmacother*; **39:** 574-575 (2005).

Hindmarch M. Interactions of the oral contraceptive pill and antibiotics and St.John's wort: knowledge of female college students. *Fam.Pract*. **19:** 708 (2002).

Hirsh J, and Hoak J. Management of deep vein thrombosis and pulmonary embolism: a statement for healthcare professionals. *Circulation.* **93:** 2212-2245 (1996).

Huang MT, Chi TH, Zhi YW, Thomas F, You-Rong L , Kathe S, Wei M, Constantino G, Jeffrey DL and Allan HC**.** Inhibition of Skin Tumorigenesis by Rosemary and Its Constituents Carnosol and Ursolic Acid. *Cancer Res.* **54:** 701-708 (1994)**.**

Ioannides C. Pharmacokinetic interactions between herbal remedies and medicinal drugs. *Xenobiotica*. **32:** 451- 478 (2002).

Ishihara K, Kushida H, Yuzurihara M, Wakui Y, Yanagisawa T, Kamei H, Ohmori S, and Kitada M. Interaction of drugs and Chinese herbs: Pharmacokinetic changes of tolbutamide and diazepam caused by extract of *Angelica dahurica*. *J. Pharm. Pharmacol.* **52:** 1023-1029 (2000).

Iwata H, Tezuka Y, Kadota S, Hiratsuka A, and Watabe T. Identification and characterization of potent CYP3A4 inhibitors in Schisandra fruit extract. *Drug. Metab. Dispos.* **32:**1351-1358 (2004).

Janetzky K, and Morreale AP. Possible interaction between warfarin and ginseng. *Am. J. Health. Syst. Pharm.* **54:**692-693 (1997).

Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO, and McLachlan AJ. Effect of St. John's wort and ginseng on pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br. J. Clin. Pharmacol*. **57:** 592-599 (2004).

Jinping Q, Peiling H, Yawei L and Abliz Z. *J. Pharm. Pharmacol*. **55:** 1163-1167 (2003).

Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, and Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clin. Pharmacol. Ther*. **66:** 338-345 (1999).

Jones BD and Runikis AM. Interaction of ginseng with phenelzine (Letter). *J. Clin. Psychopharmacol.* **7:** 201 (1987).

Kales HC, Blow FC, Welsh DE and Mellow AM. Herbal products and other supplements: use by elderly veterans with depression and dementia and their caregivers. *J Geriat. Psychiatr. Neurol*. **17**: 25-31(2004).

Kawaguchi A, Ohmori M, Tsuruoka S, Nishiki K, Harada K, Miyamori I, Yano R, Nakamura T, Masada M, and Fujimura A. Drug interaction between St. John's wort and quazepam. *Br. J. Clin. Pharmacol*. **58:** 403-410 (2004).

Kaye A, Clarke R, Sabar R, VIg S, Dhawan KP, Hofbauer R and Kaye AM. Herbal medicines: Current trends in anesthesiology practice – A hospital based survey. *J. Clin. Anesth*. **12:** 468-471(2000).

Keller F, and Klohs MW. A review of the chemistry and pharmacology of the constituents of *Piper methysticum*. *Lloydia*. **26:** 1-15(1963).

Kent UM, Aviram M, Rosenblat M, and Hollenberg PF. The licorice root derived isoflavan glabridin inhibits the activities of human cytochrome P – 450's 3A4, 2B6, and 2C9. *Drug. Metab. Dispos.* **30:** 709-715 (2002).

Khawaja IS, Marotta RF, and Lippmann SS. Herbal medicines as a factor in delirium. *Psychiatr. Serv*. **50:** 969-970 (1999).

Kleijnen J and Knipschild P. *Gikgo biloba. Lancet*. **340:** 1136-1139 (1992).

Knodell RG, Dubey RK, Wilkinson GR, and Guengerich FP. Oxidative metabolism of hexobarbital in human liver: relationship to polymorphic S-mephenytoin 4-hydroxylation. *J Pharmacol Exp Ther.* **245:** 845-849 (1988).

Kupiec T and Raj V. Fatal seizures due to potential herb-drug interactions with *Ginkgo biloba. J. Anal. Toxicol*. **29:** 755-758 (2005).

Lacombiez L, Bensimon G, and Isnard F. Effect of of yohimbine on blood pressure in patients with depression and orthostatic hypertension induced by clomipramine. *Clin. Pharmacol. Ther*. **45:** 241-251 (1989).

Lantz MS, Buchalter E, and Giambanco V. St John's wort and antidepressant drug interactions in the elderly. *J. Geriatr. Psychiatr. Neurol*. **12:** 7-10 (1999).

Lechner D, Michael S, Moyosoluwa O, Rogelio P, Miranda and Simon G. The anti-staphylococcal activity of *Angelica dahurica* (Bai Zhi). *Phytochem.* **65:** 331-335 (2004).

Lee A, Chui PT, Aun CS, Gin T and Lau AS. Possible interaction between sevoflurane and *Aloe vera*. *Ann. Pharmacother*. **38:** 1651-1654 (2004).

Ling M, Piddlesden SJ and Morgan BP. A component of the medicinal herb ephedra blocks activation in the classical and alternative pathways of complement. *Clin. Exp. Immunol.* **102:** 582-588 (1995).

Mai I, Kruger H, Budde K, Johne A, and Roots I. Hazardous pharmacokinetic inteaction of St. John's wort with the immunosupressant cyclosporine. *Inter. J. Clin. Phamacol. Ther*. **38:** 500-502 (2000).

Mai I, Stormer E, Bauer S, Kruger H, Budde K, and Roots I. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. *Nephrol. Dial. Transplant.* **18:** 819-822 (2003).

Makheja AN and Bailey JM. A platelet phospholipase inhibitor from the medicinal herb feverfew (*Tanacetum parthenium*). *Prostagland. Leukot. Med.* **8:** 653-660 (1982).

Mashour NH, Lin GI and Frishman WH. Herbal medicine for the treatment of cardiovascular disease: Clinical considerations. *Arch. Intern. Med.* **158:** 2225-2234 (1998).

Mathews JM, Etheridge AS, and Black SR. Inhibition of human cytochrome P-450 activities by kava extract and kavalactones. *Drug. Metab. Dispos.* **30:**1153-1157 (2002).

Mathews JM, Etheridge AS, Valentine JL, Black SR, Colemon, DP, Patel P, So J and Burka LT. Pharmacokinetics and disposition of the kavalactones, kawain: interaction with kava extract and kavalactones in vivo and in vitro. *Drug. Metab. Dispos.* **33:** 1555-1563 (2005).

Mathijssen RH, Verweij J, de Bruijn P, Loos WJ, and Sparreboom A. Effects of St.John's wort on irinotecan metabolism. *J. Natl. Cancer Inst.* **94:** 1247-1249 (2002).

Mauro VF, Mauro LS, Kleshinski JF, Khuder SA, Wang Y, and Erhardt PW. Impact of *Ginkgo biloba* on the pharmacokinetics of digoxin. *Am. J. Ther*. **10:** 247-251 (2003).

McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. *Can. Med. Assoc. J*. **155:** 293-295 (1996).

Meier B, Berger D, Hoberg E, Sticher O, and Schaffner W. Pharmacological activities of Vitex agnus castus in vitro. *Phytomed.* **7:** 373-381 (2000).

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

Mester L, Mester M and Nityanand S. Inhibition of platelet aggregation by guggulu steroids. *Planta Med*. **37:** 367-369 (1979).

Miller LG. Drug interactions known or potentially associated with St.John's wort. *J Herbal Pharmacother.* **1:** 51-64 (2001).

Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch. Intern. Med.* **158:** 2200-2211 (1998).

Modarai M, Gertsch J, Suter A, Heinrich M and Kortenkamp A. Cytochrome P-450 inhibitory action of Echinacea preparations differs widely and co – varies with alkylamide content. *J. Pharm. Pharmacol*. **59:** 567-573 (2007).

Morimoto, Kotegawa T , Kimiko T, Yasukiyo O, Hiromitsu I, and Shigeyuki N. Effect of St. John's Wort on the Pharmacokinetics of Theophylline in Healthy Volunteers. *Clin. Pharmacol* . **44:** 95-101 (2004).

Mostefa KN, Pauwels A, Pine E, Biour M and Levy VG. Fatal hepatitis after germander tea. *Lancet*. **340:** 1101-1104 (2000).

Mueller SC, Uehleke B, Woehling H, Petzsch M, Majcher-Peszynska J, Hehl EM, Sievers H, Frank B, Riethling AK, and Drewelow B. Effect of St. John's wort dose and preparations on the pharmacokinetics of digoxin. *Clin. Pharmacol. Ther*. **75:** 546 (2004).

Nambiar S, Schwartz RH and Constantino A. Hypertension in mother and baby linked to ingestion of Chinese herbal medicine. *West. J. Med*. **171:**152. (1999).

Nebel A, Schneider BJ, Baker RK and Kroll DJ. Potential metabolic interaction between St. John's wort and theophylline. *Ann. Pharmacother*. **33:** 502 (1999).

Newall C, Anderson LA and Phillipson JD. Herbal Medicines. Pharmaceutical Press, England. 1996.

Norred CL and Finlayson CA. Hemorrhage afer preoperative use of complementary and alternative medicines. *AANA. J.* **68:** 217-220 (2000).

Ohnishi N, Kusuhara M, Yoshioka M, Kuroda K, Soga A, Nishikawa F, Koishi T, Nakagawa M, Hori S, Matsumoto T, Yamashita M, Ohta S, Takara K, and Yokoyama T. Studies on interactions between functional foods or dietary supplements and medicines. I. Effects of *Ginkgo biloba* leaf extract on the pharmacokinetics of diltiazem in rats. *Biol. Pharm. Bull.* **26:** 1315-1320 (2003).

Panda S and Kar A. Guggulu (*Commiphora mukul*) induces triiodothyronine production: possible involvement of lipid peroxidation. *Life. Sci.* **65:** 137-141(1999).

Parker V, Wong AH, Boon HS and Seeman MV. Adverse reactions to St John's Wort. *Can. J. Psychiat.* **46:** 77-79 (2001).

Patel JA and Gohil KJ. Warfarin – herb drug interactions a review and study based on assessment of clinical case reports in literature. *Bol. Latinoam. Caribe. Plant. Med. Aromaticas.* **7:** 85-99 (2008).

Pfrunder A, Schiesser M, Geber S, Haschke M, Bitzer J and Drewe J. Interaction of St. John's wort with low-dose oral contraceptive therapy and randomized controlled trial. *Br. J. Clin. Pharmacol.* **56:** 683-690 (2003).

Piscitelli SC, Burstein AH, Welden N, Gallicano KD, and Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin. Infect. Dis.* **34:** 235-238 (2002).

Piscitelli SC, Formentini E, Burstein AH, Alfaro R, Jagannatha S, and Falloon J. Effect of milk thistle on the pharmacokinetics of indinavir in healthy volunteers. *Pharmacother*. **22:** 551-556 (2002).

Prost N, Tichadou L, Rodor F, Nguyen N, David JM, and Jean PMJ. St. John's wort venlaflaxine interaction. *Presse. Med*. **29:** 1285-1286 (2000).

Raduege KM, Kleshinski JF, Ryckman JV, and Tetzlaff JE. Anesthetic considerations of the herbal, kava. *J. Clin. Anesth.* **16:** 305-311 (2004).

Renfrew C, Dickson R, and Schwab C. Severe hypertension following ephedrine administration in a patient receiving entacapone. *Anesthesiol*. **93:** 1562 (2000).

Rivera E, Daggfeldt A, and Hu S. Ginseng extract in aluminium hydroxide adjuvanted vaccines improves the antibody response of pigs to porcine parvovirus and *Erysipelothrix rhusiopathiae*. *Vet. Immunol. Immunopathol.* **91:** 19-27 (2003).

Rose KD, Croissant PD, Parliament CF, and Levin MB. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. *Neurosurgery*.**26:** 880-882 (1990).

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

Rowin J and Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion. *Neurol*. **46:** 1775-1776 (1996).

Roy-Byrne PP, Bystritsky A, Russo J, Craske MC, Sherbourne CD and Stein MB. Use of herbal medicine in primary care patients with mood and anxiety disorders. *Psychosomat*. **46:** 117-122 (2005).

Roz N, Mazur Y, Hirshfeld A, and Rehavi M. Inhibition of vesicular uptake of monoamines by hyperforin. *Life. Sci*. **71:** 2227-2237 (2002).

Ruschitzka F, Meier PJ, Turina M, Luscher TF, and Noll G. Acute heart transplant rejection due to Saint John's wort. *Lancet*. **355:** 548-549 (2000).

Saba R, Kaye A and Frost E. perioperative considerations for the patient on herbal medicines. *Med. East. J. Anesthesiol.* **16:** 287-296(2001).

Sachiko T, Maki A, Tomohiro Y, Yuko Y, Ahmed AE, and Tomihisa. CYP3A4 Inhibitors Isolated from Licorice**.** *Biol. Pharm. Bull*. **28:** 2000-2002 (2005).

Sailler L, Juchet H, Ollier S, Nicodeme R, and Arlet P. Potassium loss may increase effects, especially of digitalis and related glycosides. *Rev. Med. Intern*. **14:** 984 (1993).

Salassa RM, Mattox VR, and Rosevear JW. Inhibition of the mineralocorticoid activity of licorice by spironolactone. *J. Endocrinol. Metab*. **22:** 1156-1159 (1962).

Samuel I and Juraj S. A Possible Cause of Cardiovascular Collapse During Anesthesia: Long-Term Use of St. John's Wort. *J. Clin. Anesth.* **12:** 498-499 (2000).

Sasaki K, Hatta S, Wada K, Itoh M, Yoshimura T, and Haga M. Bilobalide prevents reduction of gamma – amino butyric acid levels and glutamic acid decarboxylase activity induced by methylpyridone in mouse hippocampus. *Life Sci*. **67:** 709-715 (2000).

Scambia G, De Vincenzo R, Ranelletti FO, Panici PB, Ferrandina G, D'Agostino G, Fattorossi A, Bombardelli E, and Mancuso S. Antiproliferative effect of silybin on gynecological malignancies synergism with cisplatin and doxorubicin. *Eur. J. Cancer*. **32:** 877- 882 (1996).

Schelosky L, Raffauf C, Jendroska K, and Poewe W. Kava and dopamine antagonism. *J. Neurol. Neurosurg. Psychiat.* **58:** 639-640 (1995).

Schussler M, Holzl J, and Fricke U. Myocardial effects of flavonoids from *Crataegus* species. *Arzneimittel. Forschung*. **45:** 842-845 (1995).

Schwarz UI. Unwanted pregnacy on self medication with St.john's wort despite hormonal contraception. *Br. J. Clin. Pharmacol*. **55:** 112-113 (2003).

Shaw D, Leon C, Koley S and Murray AV. Traditional remedies and food supplements: a 5-year toxicological study (1991–1995). *Drug Safety*. **17:** 342-356 (1997).

Shinozuka K, Umegaki K, Kubota Y, Tanaka N, Mizuno H, Yamauchi J, Kazuki N, and Masaru K. Feeding of *Ginkgo biloba* extract(GBE) enhances gene expression of hepatic cytochrome P – 450 and attenuates the hypotensive effect of nicardipine in rats. *Life Sci.* **70:** 2783-2792 (2002).

Silvers KM, Woolley CC and Hedderley, D. Dietary supplement use in people being treated for depression. *Asia. Pac. J. Clin. Nutr*. **15:** 30-34(2006).

Spinella M. Herbal Medicines and Epilepsy: The Potential for Benefit and Adverse Effects. *Epilepsy Behav*. **2:** 524-532 (2001).

Stevinson C, Pittler MH and Ernst E. Garlic for treating hypercholesterolemia. A meta -analysis of randomized clinical trials. *Ann. Intern. Med*. **133:**420-429 (2000)

Sugimoto K, Ohmori M, Tsuruoka S, Nishiki K, Kawaguchi A, and Harada K. Different effects of St John's wort on the pharmacokinetics of simvastatin and pravastatin. *Clin Pharmacol Ther*. **70:** 518-524 (2001).

Sugiyama T, Kubota Y, Shinozuka K, Yamada S, Jian W, and Umegaki K. *Ginkgo biloba* extract modifies hypoglycaemic action of tolbutamide via hepatic cytochrome P – 450 mediated mechanism in aged rats. *Life Sci.* **75:** 1113-1122 (2004).

Susan NN, Mohammed A and Prasad SV. Pharmacodynamic interaction of *Momordica charantia* with rosiglitazone in rats. *Chem. Biol. Interac.* **177:** 247-253 (2009).

Svensson US, Ashton M, Trinh NH, Bertilsson L, Dinh XH, Nguyen VH, Nguyen TN, Nguyen DS, Lykkesfeldt J, and Le DC. Artemisinin induces omeprazole metabolism in human beings. *Clin. Pharmacol. Ther*. **64:** 160-167 (1998).

Takahashi M, and Tokuyama S. Pharmacological and psychological effects of ginseng on actions induced by opioids and psychostimulants. *Meth. Find. Exper. Clin. Pharmacol*. **20:** 77-84 (1998).

Tam LS, Chan TYK, Leung WK, and Critchley JAJH. Warfarin interactions with Chinese traditional medicines: danshen and methylsalicylate medicated oil. *Austr. NZ. J. Med.* **25:** 258 (1995).

Tania L, Brian CF, Cathy ED, Anthony K, John TA, John FL, and Scott AJ. In vitro activity of commercial valerian root extracts against human cytochrome P-450 3A4. *J. Pharm.Pharmaceut. Sci.* **7:** 265-273 (2004).

Tankanow R, Tamer HR, Streetman DS, Smith SG, Welton JL, Annesley T, Aaronson KD, and Bleske BE. Interaction study between digoxin and a preparation of hawthorn (*Crataegus oxyacantha*). *J. Clin. Pharmacol*. **43:** 637-644 (2003).

Tannergren C, Engman H, Knutson L, Hedeland M, Bondesson U, and Lennernas H. 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 (2004).

Taylor JR, and Wilt VM. Probable antagonism of warfarin by green tea. *Ann. Pharmacother*. **33:** 426 (1999).

Turan I and Martorano D. Natural substances in psychiatry (*Ginkgo biloba* in dementia). *Pharmacol Bull*.**31:**147-158 (1995).

Usia T, Watabe T, Kadota S, and Tezuka Y. Cytochrome P-4502D6(CYP2D6) inhibitory constituents of *Catharanthus roseus*. *Biol Pharm Bull*. **28:** 1021-1024 (2005).

Vattanajun A, Watanabe H, Tantisara MH, and Tantisara B. Isobolographically additive anticonvulsant activity between *Centella asiatica's* ethyl acetate fraction and some antiepileptic drugs. *J. Med. Assoc. Thai*. 88: 131-140 (2005).

Venkataramanan R, Ramachandran V, Komoroski BJ, Zhang S, Schiff PL, and Strom SC. Milk thistle, a herbal supplement, decreases the activity of CYP3A4 and uridine diphosphoglucuronosyl transferase in human hepatocyte cultures. *Drug. Metab. Dispos.* **28:**1270-1273 (2000).

Vladimir K, and Daniela W. Silybin and Silymarin – New effects and applications. *Biomed. Papers*. **149:** 29-41 (2005).

Wang J, Xu R, Chen Z, and Fidler JM. Immunosuppressive activity of Chinese medicinal plant *Tripterygium wilfordi*. Prolongation of rat cardiac and renal allograft survival by the PG27 extract and immunosuppressive synergy in combination with cyclosporine. *Transplant.* **70:** 447-455 (2000).

Willey LB, Mady SP, Cobaugh DJ, and Wax PM. Valerian overdose: a case report. *Vet Hum. Toxicol*. **37:** 364-365 (1995).

William HF, Stephen TS and Mohammed M. The use of herbs for treating cardiovascular disease. *Sem. Integ. Med* .**2:** 23-35 (2004).

Wong AH, Smith M, and Boon HS. Herbal remedies in psychiatric practice. *Arch Gen Psychiatry*. **55:** 1033-1044 (1998).

Yadhu NS. Potential for interaction of kava and St. John's wort with drugs. *J Ethnopharmacol.* **100:** 108-113 (2005).

Yale SH, and Glurich I. Analysis of the inhibitory potential of *Ginkgo biloba*, *Echinacea purpurea*, and *Sernoa repens* on the metabolic activity of cytochrome P-4503A4, 2D6 and 2C9. *J. Altern. Complement. Med*. **11:** 433-439 (2005).

Yeoh KG, Kang JY, Yap I, Guan R, Tan CC, Wee A, and Teng CH. Chilli protects against aspirin-induced gastro duodenal mucosal injury in humans. *Dig. Dis. Sci.* **40:** 580-583 (1995).

Yin OQ, Tomlinson B, Waye MM, Chow AH, and Chow MS. Pharmacogenetics and herb-drug interactions: experience with *Ginkgo biloba* and omeprazole. *Pharmacogen.* **14:** 841-850 (2004).

Zhang XY, Zhou DF, Zhang PY, Wu GY, Su JM, and Cao LY. A double-blind, placebo-controlled trial of extract of Ginkgo biloba added to haloperidol in treatment-resistant patients with schizophrenia. *J. Clin. Psych*. **62:** 878-883 (2001).

Zhou MX. Therapeutic effect of astragalus in treating chronic active hepatitis and the changes in immune function. *J. Chin. People's Liber. Army*.**7:** 242-244 (1982).

Zhu M, Wong PY, and Li RC. Effect of oral administration of fennel (*Foeniculum vulgare)* on ciprofloxacin absorption and disposition in the rat. *J. Pharm. Pharmacol.* **51:** 1391-1396 (1999).