Herb drug interactions

Akanksha Yadav, Awan kumar Pandey

S.N. college of pharmacy

ABSTRACT

It is the Millions of people today use herbs either as food or in the form of medicine along with prescription and non prescription medications. Although considered natural and safe, many of these herbs can interact with other medications, causing either potentially dangerous side effects and/or reduced benefits from the medication. Both pharmacokinetic and pharmacodynamic mechanisms are involved in these interactions and majority of the herb-drug interactions were found to be mediated by metabolic inductions or inhibitions. It should be understood that herbal preparations contain multiple active photochemical in varying proportions which can, like any other active pharmacological substance, alter the enzymatic systems, transporters and/or the physiologic processes. The purpose of this review is to discuss evidence based mechanisms and clinical implications of such herb-drug interactions and to increase awareness on herb-drug interactions by reviewing published clinical and preclinical studies. As the incidence and severity of herb-drug interactions is increasing due to a worldwide rise in the use of herbal preparations, more clinical data regarding herb-drug interactions are needed to make decisions regarding patient safety. The increasing understanding of pharmacokinetic herbdrug interactions will make health care professionals and patients pay more attention to the potential interactions.

Keywords: *Herb-Drug Interaction, Mechanism, CYP, P-gp, Clinical implications*

INTRODUCTION:

It is the term of „Herbal products‟ has become a colloquial term which is commonly refers to all types of preparations obtained from herbs, spices, roots, stems, leaves and other non botanical materials of natural origin. They can be used therapeutically as prescription or over-the counter medicines or even as food . Due to high prices and potential side effects of synthetic drugs, people rely more on herbal drugs and this trend is growing, not only in developing countries but in developed countries too.

This upsurge in the use of phytomedicines is a global phenomenon, with more than 80% of people in Africa and Asia using herbal medicines and an increasing number in the Western world. It is estimated that 60 to 70% of the Americans are using herbal products . According to WHO estimates, demand for medicinal plants by the year 2050 would be ~US $5 trillion .

Where one of the consequences of concurrent use of herbal medicines and allopathic drugs is the possibility of interactions. The interaction of drugs with herbal medicines is a significant safety concern, especially for drugs with narrow therapeutic indices (e.g. warfarin and digoxin), drugs with long-term regimens and which are used in the management of life threatening conditions. The risk of adverse effects due to interactions between herbal products and conventional drugs is often underestimated 4 by consumers due to lack of information on the safety of herbal preparations.

It has become very difficult to identify the possibility of occurrence of an interaction due to

☐ Availability and easy accessibility of large number of herbal products in the market

☐ Lack of data on the pharmacological action and mechanisms of interactions of herbal products 4

☐ Misinformation on the actual label content of herbal products 4, 5

☐ Presence of multiple components of various pharmacological properties in the herbs

☐ Low potential of herb induced adverse effects

Further more, clinical trials addressing the safety and risk of co-administered drugs with certain herbal products showed that the outcomes are greatly affected by pharmacogenetics and/or individual variability 6, 7. Due to the clinical significance of herbal interactions with conventional drugs, it is important to identify herbs and drugs that may interact with each other. This paper updates our knowledge on herb-drug interactions with an emphasis on mechanistic and clinical considerations.

2. Mechanisms Involved in Herb-Drug Interactions:

When are Knowledge of the mechanism by which a given herb-drug interaction occurs is often clinical useful, since the mechanism may influence both the time course and methods of circumventing the interaction. Herb–drug interactions based on the mechanism involved are classified into pharmacokinetic and pharmacodynamic interactions.

2.1 Pharmacokinetic interactions:

Pharmacokinetic interactions are caused by alterations in the absorption, distribution, metabolism, or excretion (ADME) of drugs which are results in altered levels of the drug or its metabolites.

2.1.1 Herb-drug interactions at absorption level

2.1.1.(a) Influence of herbs on efflux transporters:

Several reports have indicated that human drug efflux transporters, acting alone or together with drug metabolising enzymes, play an important role in oral drug bioavailability 8. Efflux of drugs against a steep concentration gradient is mediated by the ATP binding cassette (ABC) transporters, mostly located in the canalicular membrane of the intestinal epithelium, human liver, kidney or the endothelium of blood capillaries of the brain . ABC transporters are relatively easily modulated by factors such as therapeutic drugs and herbal medicines, foods and beverages .

The efflux transporters play a role in limiting influx of xenobiotics, thus preventing the intracellular accumulation of their own substrates. The activity of the efflux transporters on interaction with herbs may be inhibited by competitive or noncompetitive mechanisms, which may potentially lead to toxic blood plasma concentrations of drugs that are normally substrates. Conversely, the induction of efflux transporters by herbs would result in sub-therapeutic plasma drug levels leading to treatment failure .

The mechanisms and examples of influence of the herbs on different efflux transporters is explained as follows.

P- Glyco protein (P-gp):

P-gp is also known as multi-drug resistance protein 1 (MDR1) or ABC subfamily B, member 1 12. PGlycoprotein has a significant role in oral drug absorption and decreases bioavailability because intact drug molecules are pumped back into the gastrointestinal tract lumen and exposed multiple times to enterocyte metabolism using ATP as an energy source. Within hepatocytes, P-gp mostly pumps hydrophobic (neutral or positively charged) substances into the bile and this efflux occurs in many other organs such as the kidney as well 12. Pgp plays an important role in regulating the absorption, distribution and elimination/ reabsorption of many clinically important therapeutic substances. Modulation of P-gp by herbal constituents may, therefore, involve direct interaction with one or more binding sites on the p-gp molecule through competitive or noncompetitive inhibition or induction of the efflux of drugs. Phytochemicals may also inhibit ATP binding, hydrolysis or coupling of ATP-hydrolysed molecules, therefore, depleting the energy which drives the translocation of P-gp bound substrate drugs 7 . Phytoconstituents that induce P-gp will in turn potentiate the substrate-induced-fit of drugs resulting in even much higher efflux of most P-gp substrates 13 .

Some examples of herb drug interactionsϖ modulated by P- gp:

- P-glycoprotein confers high levels of¬ resistance to bulky amphipathic natural product type drugs such as paclitaxel, Vinca alkaloids, anthracyclines, camptothecins, and epipodophyllotoxins. Alisol B23-acetate from Alisma orientalis has increased anticancer activity of vinblastine, doxorubicin, rhodamine-123 by reducing P-gp efflux activity in vitro in MDR cell lines (HepG2-DR and K562-DR) 14
- Camellia sinensis (green tea) contains¬ catechins that modulate P-gp transport in vitro and in vivo either through inhibition or activation by means of a heterotropic allosteric mechanism 22. 6-gingerol inhibited P-gp-mediated efflux of daunorubicin and rhodamine-123 in KBC2 cells 23 . The in vitro or in vivo activity of human P-gp was significantly reduced by Ginkgo biloba (ginkgo) extract 8 .
- A few divergent results on the¬ modulation of P-gp by Allium sativum (garlic) have been reported. Aged garlic extract has been shown to induce P-gp, MRP2, BCRP and OATPs activities 19 . The diallyl sulphide which is an active constituent in garlic can also induce P-gp and MRP2 expression in vitro 20 . Interestingly, diallyl trisulfide has been shown to inhibit the activity and expression of P-gp in a recent study 21 .
- Citrus paradisi (Grapefruit juice) was¬ found to inhibit P-gp rhodamine-123 efflux in vitro in Caco-2 cells 15 and in vivo in healthy volunteers 16. It was also found to increase the bioavailability of nifedipine in vivo in rats 17 and talinolol in vitro in Caco-2 cells.

Other drug efflux transporters:

(ii) Multi-drug resistance-associated protein-2 (MRP2):

MRP2 or ABC subfamily C member 2 (ABCC2) is functionally a canalicular multi-specific organic anion transporter 11. MRP2 is localised in the bile canalicular membrane of hepatocytes and part of the 9-member human subfamily of multi-drug resistance-associated proteins (MRP1 - MRP9). The expression of MRP2, unlike P-gp, is high in the proximal and very low in the distal region of human intestines 11. MRP2 is found in many cancer cell lines and tumours obtained from patients suggesting that MRP2 may contribute to resistance against treatment with chemotherapeutic drugs.

The ATP-dependent MRP family primarily transports hydrophobic anionic conjugates and extrudes hydrophobic neutral molecules. In particular, MRP2 exports relatively large hydrophilic compounds including the glucuronide, glutathione and sulfate conjugates of endogenous and exogenous compounds from liver cells into the bile 12. MRP2 is also responsible for the biliary secretion of organic anions such as acetaminophen glucuronide and camptothecin 24 .

(iii) Breast cancer resistance protein (BCRP):

Another important drug efflux transporter is the breast cancer resistance protein (BCRP), member 2 on the ABC White (ABCG) subfamily, which contains „half-transporters" 25. BCRP or ABCG2 is also known as placenta-specific ABC gene or as mitoxantrone resistance gene. BCRP is expressed in a variety of tumour cells and many normal human tissues. BCRP has only one nucleotide binding domain, namely the ABC at the amine terminus and a single set of transmembrane domain containing six transmembrane regions at the carboxyl terminus . BCRP confers resistance to a narrower range of anticancer agents than Pglycoprotein and MRP.

Some examples of herb drug interactionsϖ modulated by MRP2 and BCRP:

Relatively little information about the effects¬ of herbal products on efflux transporters other than P-gp is available. However, herbs that show ability to modulate P-gp activity may also affect related efflux transporters. For instance, herbs with interactions that occur by the same pathway as grapefruit juice may also modulate MRP2 and BCRP. It is, therefore, suggested that more in vitro and in vivo data are required to be conclusive in terms of the significance of these pathways of herb--drug pharmacokinetic interactions on the bioavailability and consequently on the pharmacological effect and toxicity of affected drugs.

Cooray et al. report that some plant-derived¬ polyphenols that interact with P-gp can also modulate BCRP activity in vitro 27 . Meanwhile, it was reported that flavonoids like apigenin, biochanin A, genistein, kaempferol from Silybum marianum enhance the accumulation of the BCRP substrate mitoxantrone by inhibition of BCRP in vitro and in vivo

in MCF-7 M-X100 cells 28 On the other hand, BCRP does not confer resistance to the Vinca alkaloids, epipodophyllotoxins, paclitaxel, or cisplatin.

(iv) Influence of herbs on uptake carrier proteins

SLC transporters such as organic anion transporters OATs), organic cation transporters (OCTs) and organic anion transporting polypeptides (OATPs) mainly mediate uptake of substrates in cells. These transporters are involved in oral bioavailability and intestinal, hepatobiliary and renal excretion of a concomitant drug.**:**

Examples

- Inhibition of OATP1 and OATP3 by components of Citrus sinensis (Seville orange) and Malus domestica (apple) juices may decrease drug uptake and lead to subtherapeutic drug concentrations in vitro and in vivo 33. On the other hand, Takano et al. suggest that over-induction of OATP may increase drug uptake and lead to toxic blood drug concentrations 11.
- Naringin, a furanocoumarinic phytochemical in Citrus paradisi juice, inhibits the influx or uptake active transporter organic anion transporting polypeptide (OATP) 1A2 in vitro consequently lowering the bioavailability of certain drugs 30, 31. A polyphenolic catechin,epigallocatechin gallate found in Citrus sinensis and Echinacea purpurea (Echinacea), showed potential to inhibit OATP-B in vitro resulting in reduced drug carrier-mediated transport into the cell possibly lowering drug bioavailability .

2.1.1.(b) Herb interactions on gastrointestinal motility:

Altered gastrointestinal motility following consumption of herbal products can have a marked impact on the therapeutic outcomes of treatment with conventional drugs. Herbal induced diarrhoea, which results in a shorter transit time of the drug along the gastrointestinal tract, reduces contact time with the gastrointestinal epithelium and, therefore, leads to lower drug absorption.

Ginkgo biloba leaf extract containing¬ flavonoids and terpenoids, Zingiber officinale (ginger) and Piper methysticum (kava) extracts increase gastrointestinal motility in vitro and in vivo . Echinacea purpurea and Hypericum perforatum which are known to induce diarrhoea as side effects may also affect drug absorption in a similar manner . Sennosides were found to increase the GIT transit rate and motility in vitro in mouse colon cells and Caco-2 cells respectively. The herbs can also increase the activity of laxatives indicated for constipation and antagonise the action of antidiarrhoeal agents

2.1.1.(c) Herb interactions through complex formation

When the formation of insoluble herb-drug complexes in the gastrointestinal tract can significantly reduce the bioavailability of co-administered drugs resulting in sub-therapeutic effects. Some antibiotics such as flouroquinolones and tetracyclines bind to iron, calcium, calcium-fortified foods and supplements including herbal products and co-administered antacids.

The formation of herb-drug complexes implies that the emergence of resistance in the treatment of diseases like tuberculosis and HIV/AIDS may have long-term implications on the quality-adjusted life years of the patient. An example is that of phenytoin that may bind to iron, calcium and magnesium in antacids and herbal preparations resulting in possible injuries due to uncontrolled epilepsy.

Examples:

The Fibres such as psyllium and alginates may¬ chelate iron and drugs such as metformin and glibenclamide as shown by both in vitro and in vivo studies, thus, reducing their clinical efficacy. For instance, the absorption of iron from an iron-fortified meal was significantly reduced by Capsicum annum 37. The authors postulated that the reduction in iron absorption was due to iron binding to chilli polyphenols such as capsaicin. In view of the potential chelating and complexation effects of mineral components in certain herbal preparations, they should be administered either 2 h before or 2 h after the dose of the interacting drug. The effect of herbs on pharmacokinetics of drugs via the mechanism of complex formation remains inconclusive due to a lack of in vivo clinical trials on this specific type of herb-drug interaction.

2.1.2 Herb-drug interactions at metabolism level

Metabolism-mediated herb-drug interactions are performed primarily by the cytochrome P450 (CYP) family of metabolic enzymes (phase I enzymes) and non CYP enzyme systems (phase II enzymes) such as uridine diphosphoglucuronosyl transferases (UGTs). Pharmacokinetic herb-drug interactions occur when drug metabolic enzymes are induced or inhibited by concomitant herbal medicines 38. Inhibition of metabolic enzymes occurs when herbal medicines are able to decrease the expression or activities of metabolic enzymes in a competitive or non-competitive manner. Induction of metabolic enzymes is a much slower process, in which herbal medicines promote gene activation and increase the gene or protein levels of the relevant metabolic enzyme. The CYPs induction is modulated by ligand-dependent transcription activation of nuclear receptors including pregnane X receptors (PXR) and constitutive androstane receptors (CAR), etc. The inhibition and induction process of enzymes are reversible and enzyme levels can return to the normal levels after stopping the administration of herbal medicines .

Examples of enzyme induction:

Induction of CYP enzymes often results in¬ therapeutic failure because of lower plasma concentrations of the drugs. One of the well-studied herb medicines, St. Johns Wort (Hypericium perforatum) induces CYP3A4 and CYP2B6, resulting in a decrease in plasma levels of irinotecan and imatinib, which are two chemotherapeutic drugs. Hyperforin, a major active ingredient of St. John"s wort, is the agonist of PXR which can modulate CYP3A4 expression . In mouse, the administration of garlic juice for 8 days induced the protein expression of CYP1A2 and 2E1 . In human, the in vivo activity of CYP3A4 was increased, by ginkgo extract .

Examples of enzyme inhibition:

In general, inhibition of CYP enzymes¬ would lead to an increase in plasma concentrations of the concomitant drug, and recognizable, increased toxicity. Furano coumarins (e.g., naringenin and bergamottin) in C. paradisi juice and C. sinensis increase the plasma concentration of a number of drugs including cyclosporine, terfenadine, midazolam and felodipine through mechanism-based inhibition of the CYP3A4 enzyme as „suicide substrate" in vitro and in vivo in humans .

Garlic extract inhibited in vitro CYP2C9,¬ 2CY2C19, CYP3A4, 3A5, and 3A7 aactivity, while it did not affect the CYP2D6 activity, and increased the activity in recombinant human CYP isozyme system.

The in vitro activities of CYP1A2, 2C9, and¬ 2E1 were decreased by ginkgo extract. The activity of CYP1A2 and 2C9 was not significantly changed by ginkgolides, while that of CYP3A4 was increased by ginkgolide A via pregnane X receptor . Ginger extract inhibited CYP2C9 and 3A4¬ activities in recombinant human CYP isozyme system 46 and CYP2C19 activity in human liver microsomes.

2.1.3 Herb-drug interactions at distribution level:

 Herbs such as meadowsweet and black willow, which contain pain-reducing salicylates, may displace highly protein bound drugs such as warfarin and carbamazepine, thus increasing the adverse effects of these drugs. These products should not be taken concurrently.

2.1.4 Herb-drug interactions at elimination level:

The major routes for elimination of drugs remain the kidney and bile, but there are no significant herb-drug interactions through bile elimination. Drugs that are chiefly excreted by the kidneys can get involved in herb-drug interactions by different mechanisms such as competition at active transport sites, or alterations in glomerular filtration, passive renal tubular reabsorption or active secretion and urinary pH. The mechanism of herbal diuresis is complex and non-uniform. Certain herbs increase the glomerular filtration rate but do not stimulate electrolyte secretion while some others act as direct tubular irritants .

Some examples of herbs capable of interacting with renal functions and drug elimination are: Impila (Callilepis laureola) causes damage to the proximal convoluted tubules and the loop of henle and was found to be be hepatotoxic . Uva ursi (Arctostaphylos uva ursi), goldenrod (Solidago virgaurea), dandelion (Taraxacum officinale), juniper berry (Juniperus communis), horsetail (Equisetum arvense), lovage root (Levisticum officinale), parsley (Petroselinum

crispum), asparagus root (Asparagus officinalis), stinging nettle leaf (Urtica dioica), alfalfa (Medicago sativa) were found to have diuretic property and may increase the renal elimination of other drugs .

2.2 Pharmacodynamic interactions:

Pharmacodynamic interactions are those herb-drug interactions that cause changes in pharmacological responses (e.g., changes in the physiological effect and mechanism of action of the drug on the body and altered relationship of the drug concentration to drug action). Pharmacodynamic interactions may result in augmentation or inhibition of the pharmacological activity of a co-administered drug. Herb-drug pharmacodynamic interactions would, therefore, involve changes in the pharmacological effects of the drug through additive, synergistic or antagonistic actions.

The problem lies in the fact that any single herbal preparation may contain several components, all of which may have unknown biological activities; therefore, an herbal medicine can potentially mimic, increase, or reduce the effects of coadministered drugs through simultaneous effects on the same drug targets . Unfavorable effects may incur, causing target toxicity, if the effect of the drug in combination with the herbal medicine is enhanced synergistically or by additive effects; this has been observed clinically with the anticoagulant warfarin.

In contrast, herbal medicines may contain antagonistic components, which would reduce drug efficacy and cause potential therapeutic failure as with statin therapies. Acting on or competition for the same drug target is the cause of synergistic or antagonistic effects between herbal medicines and drugs that are co-administered. For example, herbal medicines such as garlic, ginger, ginkgo, ginseng, alfalfa (Medicago sativa), chamomile (Matricaria recutita), and danshen may enhance the anticoagulant activity of warfarin by targeting the same vitamin K epoxide reductase target or other critical components in the coagulation cascade . Thus, all of these herbal products may increase the risk of bleeding in patients on chronic warfarin therapy. Aspilia africana (Alkaloids, tannins) when used along with artemisinin, chloroquine in malaria was found to antagonise their effects.

3. Clinical Outcomes of Herb-Drug Interactions:

When a drug‟s clearance is significantly altered, or its drug targets are the same as the herbal components, a clinically important herbal interaction with the drug may occur. The clinical outcome of an herb-drug interaction varies, being well tolerated, mild, or sometimes lethal.

3.1 Altered Drug Clearance:

Herbal medicines that are able to modulate intestinal and hepatic CYPs and P-gp often alter the oral absorption, bioavailability, systemic exposure and clearance of co administered drugs .

For example, Milk thistle that contains potent¬ CYP3A4, BCRP and P-gp inhibitor (silibins and silymarin) and would increase the oral bioavailability and decrease the clearance of co administered drugs. In studies on the effect of its active component silibinin on the pharmacokinetics of the anti-tuberculous drug pyrazinamide, Wu and Tsai suggested that the herb altered the hepatobiliary elimination of pyrazinamide . Rajnarayana et al., showed that another component, silymarin caused an increased clearance of metronidazole and its metabolite hydroxymetronidazole, thereby decreasing the half life of this antiprotozoal agent . Garlic preparations decrease the plasma concentrations of saquinavir. Consequently, drug efficacy may be changed and toxicity may occur.

3.2 Altered Drug Efficacy:

There are limited clinical studies addressing the effect of combined herbal medicines on drug efficacy due to pharmacokinetic and/or pharmacodynamic mechanisms. When the systemic exposure of a drug is significantly increased or reduced by herbal medicines, the clinical response to this drug may change. A direct additive, synergistic or antagonistic interaction between the drug and herbal medicines will also alter the magnitude of drug response.

Many herbal medicines such as. Danshen¬ (Salvia miltiorrhiza), dong quai(Angelica sinensis), fever few (Tanacetum parthenium goldenseal (Hydrastis canadensis), ginseng, horse chestnut (Aesculus hippocastanum), red clover

(Trifolium pratense), tumeric, passionflower (Passiflora incarnata), and ginkgo can enhance the anticoagulant effect of warfarin .

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..

3.3 Occurrence of Adverse Effects:

An herb-drug interaction may lead to adverse reactions that may be mild, moderate, or even lifethreatening. Mild to moderate adverse events due to herb-drug interactions are generally well tolerated, but some herb-drug interactions may cause severe adverse reactions. For most of the harmful interactions, pharmacodynamic mechanism may provide an explanation, although altered pharmacokinetics may also contribute to the interactions. The clinical outcome of herb-drug interactions depends on factors that are related to the co-administered drug, herbal medicine and patients.

Generally, a doubling or more in drug plasma concentration has the potential for enhanced drug effects and/or appearance of adverse effects. However, less marked changes may still be clinically important for drugs with a steep concentration-response relationship or a narrow therapeutic index (e.g. warfarin). In most cases, the magnitude of herb-drug interactions varies markedly among individuals, depending on interindividual differences in the expression, activity of drug metabolizing enzymes and transporters, comedication with other drugs, age and many of other physiopathological factors.

There are several reports where ginseng¬ induced mania when used concomitantly with phenelzine 59 and ginkgo raised blood pressure when combined with a thiazide diuretic 60 and caused coma when combined with trazodone, an atypical antidepressant .

- Kava (Piper methysticum) caused a¬ semicomatose state when given concomitantly with alprazolam. A patient with Parkinson‟s disease taking levodopa in combination with kava had increased duration and number of "off" periods 63. This may be explained by the dopamine antagonistic activity of kava.

- Ephedra is known to have risk of myocardial¬ ischemia, tachycardia, hypertension and it may also produce ventricular arrhythmias when combined with anesthetics .

- Enhanced anticoagulation and bleeding was¬ observed when patients on chronic warfarin therapy consumed danshen (S. miltiorrhiza)

4. Patient Counseling about Herb-Drug Interactions:

Use of herbal and dietary supplements is extremely common. In one US survey of adults who regularly take prescription medication, 18·4% reported the concurrent use of at least one herbal product or high-dose vitamin. A survey of 515 users of herbal remedies in the UK found that 26% would consult their general practitioner for a serious adverse drug reaction associated with a conventional over the counter medicine, but not for a similar reaction to a herbal remedy . Clinicians must ask patients about their use of herbs in a non-judgmental, relaxed way. A disapproving manner will ensure only that a patient will conceal further use. The patient should be treated as a partner in watching out for adverse reactions or interactions and should be told about the lack of information on interactions and the need for open communication about the use of herbal remedies. Formulation, brand, dose and reason for use of herbs should be documented on the patient‟s charts and updated regularly .

5. The Other Side of Herb – Drug Interaction

Beneficial effects:

A long 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 66. 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 .

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. It is also proven that garlic prevents the formation of toxic metabolites of paracetamol, coadministration of ginkgo with antipsychotics (haloperidol) in chronic schizophrenic patients reduces extra pyramidal side effects associated with haloperidol .

Centella asiatica can also be used as an adjunctive medication for patients with epilepsy due to its additive anticonvulsant activity. 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 70. 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 .

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 . Further, studies also prove that Rosemary (Rosmarinus officinalis) has chemopreventive effect as it increases efflux and intracellular accumulation of doxorubicin and vinblastine. In vitro studies also revealed that silybinin enhances the antitumour activity of cisplatin . 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:

Drug-herb interactions listed in Table 1 have provided evidence that co-administration of prescribed medicines and herbal products could lead to serious adverse reactions caused by interactions. While potential for interaction remains low for many herbs, there are some which have demonstrated moderate to high potential. There is therefore a necessity for adequate pharmacovigilance to be carried out in minimizing unanticipated but often preventable drug-herb interactions. During the course of drug treatment, patients should be encouraged to tell their health care providers which herbal remedies they are taking, and the health care providers should be sufficiently informed to provide useful advice for their patients. Availability and application of this information is critical, particularly in elderly patients who are at higher risk of adverse interactions, especially as polypharmacy is often practised in this population (Klotz, 2009). Thus, increased knowledge of drug-herb interactions would enable health care providers and patients to be alert to the potential of interactions, and to improve the treatment outcomes.

REFFRENCE:

1) Aruna D, Maidu MU. Pharmacodynamic interaction studies of Ginkgo biloba with cilostazol and clopidogrel in healthy human subjects. Br J Clin Pharmacol. 2006;63:333-338.
2) Attele AS, Wu JA, Yuan CS. Ginseng pharmacology: multiple constituents and multiple actions. Biochem Pharmacol. 1999;58:1685-1693.

3) Bauer S, Störmer E, Johne A, Krüger H, Budde K, Neumayer HH, Roots I, Mai I. Alterations in cyclosporinA pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. Br J Clin Pharmacol. 2003;55:203-211.

4) Becker BN, Greene J, Evanson J, Chidsey G, Stone WJ. Ginseng-induced diuretic resistance. JAMA. 1996;276:606-607.

5) Beckert BW, Concannon MJ, Henry SL, Smith DS, Puckett CL. Drug interactions with herbal remedies

6) 6 TANG / www.e-tang.org   2014 / Volume 4 / Issue 3 / e17The effect of herbal medicines on platelet function: an in vivo experiment and review of the literature. Plast Reconstr Surg. 2007;120:2044-2050.

7) Black DJ, Kunze KL, Wienkers LC, Gidal BE, Seaton TL, McDonnell ND, Evans JS, Bauwens JE, TragerWF. Warfarin-fluconazole. II. A metabolically based drug interaction: in vivo studies. Drug Metab Dispos.1996;24:422-428.

8) Block E. The chemistry of garlic and onions. Sci Am. 1985;252:114-119.

9) Bone KM. Potential interaction of Ginkgo biloba leaf with antiplatelet or anticoagulant drugs: what is the evidence? Mol Nutr Food Res. 2008;52:764-771.

10) Bonetto N, Santelli L, Battistin L, Cagnin A. Serotonin syndrome and rhabdomyolysis induced by concomitant use of triptans, fluoxetine and Hypericum. Cephalalgia. 2007;27:1421-1423.

11) Borrelli F, Capasso R, Izzo AA. Garlic (Allium sativum L.): adverse effects and drug interactions in humans. Mol Nutr Food Res. 2007;51:1386-1397.

12) Boruban MC, Yasar U, Babaoglu MO, Sencan O, Bozkurt A. Tamoxifen inhibits cytochrome P450 2C9 activity in breastcancer patients. J Chemother. 2006;18:421-424.

13) Butterweck V, Schmidt M. St John's wort: role of active compounds for its mechanism of action and efficacy. Wien Med Wochenschr. 2007;157:356-361.

14) Chan K, Lo AC, Yeung JH, Woo KS. The effects of Danshen (Salvia miltiorrhiza) on warfarin pharmacodynamics and pharmacokinetics of warfarin enantiomers in rats. J Pharm Pharmacol. 1995;47:402-406.

15) Chang TK, Chen J, Benetton SA. In vitro effect of standardized ginseng extracts and individual ginsenosides on the catalytic activity of human CYP1A1, CYP1A2, and CYP1B1. Drug Metab Dispos. 2002;30:378-384.

16) Cheng TO. Cardiovascular effects of Danshen. Int J Cardiol. 2007;121:9-22.

17) Cox MC, Low J, Lee J, Walshe J, Denduluri N, Berman A, Permenter MG, Petros WP, Price DK,Figg WD, Sparreboom A, Swain SM. Influence of garlic (Allium sativum) on the pharmacokinetics of docetaxel. Clin Cancer Res. 2006;12:4636-4640.

18) Dannawi M. Possible serotonin syndrome after combination of buspirone and St John's wort. J Psychopharmacol. 2002;16:401.

19) DeFeudis FV, Drieu K. Ginkgo biloba extract (EGb 761) and CNS functions: basic studies and clinical applications. Curr Drug Targets. 2000;1:25-58.

20) deMaat MM, Hoetelmans RM, Math t RA, van Gorp EC, Meenhorst PL, Mulder JW, Beijnen JH. Drug interaction between St John's wort and nevirapine. AIDS. 2001;15:420-421.

21) Deng JF. Clinical and laboratory investigations in herbal poisonings. Toxicology. 2002;181-182:571-576

22) Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet. 2000;38:41-57.

23) Foster BC, Vandenhoek S, Tang R, Budzinski JW, Krantis A, Li KY. Effect of several Chinese natural health products of human cytochrome P450 metabolism. J Pharm Pharm Sci. 2002;5:185-189.

24) Gallicano K, Foster B, Choudhri S. Effect of short-term administration of garlic supplements on single-dose ritonavir pharmacokinetics in healthy volunteers. Br J Clin Pharmacol. 2003;55:199-202.

25) Gao S, Liu Z, Li H, Little PJ, Liu P, Xu S. Cardiovascular actions and therapeutic potential of tanshinone IIA. Atherosclerosis. 2012;220:3-10.

26) Greenblatt DJ, von Moltke LL, Luo Y, Perloff ES, Horan KA, Bruce A, Reynolds RC, Harmatz JS, Avula B, Khan IA, Goldman P. Ginkgo biloba does not alter clearance of flurbiprofen, a cytochrome P450-2C9 substrate. J Clin Pharmacol. 2006;46:214-221.

27) Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui Y, Ang CY. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. Clin Pharmacol Ther. 2002;72:276-287.

28) Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui Y, Ang CY. Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly: St John's wort, garlic oil, Panax ginseng and Ginkgo biloba. Drugs Aging. 2005;22:525-539.

29) Hafner V, Jäger M, Matthée AK, Ding R, Burhenne J, Haefeli WE, Mikus G. Effect of simultaneous induction andinhibition of CYP3A by St John's wort and ritonavir on CYP3A activity. Clin Pharmacol Ther. 2010;87:191-196.

30) He N, Xie HG, Collins X, Edeki T, Yan Z. Effects of individual ginsenosides, ginkgolides and flavonoids on CYP2C19 and CYP2D6 activity in human liver microsomes. Clin Exp Pharmacol Physiol. 2006;33:813-815.

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

32) Izzat MB, Yim AP, El-Zufari MH. A taste of Chinese medicine!. Ann Thorac Surg. 1998;66:941-942.

33) Izzo AA, Borrelli F, Capasso R. Herbal medicine: the dangers of drug interaction. Trends Pharmacol Sci. 2002;23:358-391.

34) Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Heath Syst Pharm. 1997;54:692-693.

35) Kauffman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States. JAMA. 2002;287:337-344.

36) Kremers P. In vitro tests for predicting drug-drug interactions: the need for validated procedures. Pharmacol Toxicol. 2002;91:209-217.

37) Kuo SC, Teng CM, Leed JC, Ko FN, Chen SC, Wu TS. Antiplatelet components in Panax ginseng. Planta Med. 1990;56:164-167.

38) Kuo YH, Lin YL, Don MJ, Chen RM, Ueng YF. Induction of cytochrome P450-dependent monooxygenase by extracts of the medicinal herb Salvia miltiorrhiza. J Pharm Pharmacol. 2006;58:521-527.

39) Lam FF, Yeung JH, Cheung JH, Or PM. Pharmacological evidence for calcium channel inhibition by Danshen (Salvia miltiorrhiza) on rat isolated femoral artery. J Cardiovasc Pharmacol. 2006;47:139-145.

40) Lei HP, Ji W, Lin J, Chen H, Tan ZR, Hu DL, Liu LJ, Zhou HH. Effects of Ginkgo biloba extract on the pharmacokinetics of bupropion in healthy volunteers. Br J Clin Pharmacol. 2009;68:201-206.

41) Linde K, Berner MM, Kriston L. St. John's wort for major depression. Cochrane Database Syst Rev. 2008;CD000448.

42) Lo AC, Chan K, Yeung JH, Woo KS. The effects of Danshen (Salvia miltiorrhiza) on pharmacokinetics and pharmacodynamics of warfarin in rats. Eur J Drug Metab Pharmacokinet. 1992;17:257-262.

43) Mai I, Bauer S, Perloff ES, Johne A, Uehleke B, Frank B, Budde K, Roots I. Hyperforin content determines the magnitude of the St John's wort-cyclosporine drug interaction. Clin Pharmacol Ther. 2004;76:330-340.

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

45) Markowitz JS, Donovan JL, Lindsay DeVane C, Sipkes L,Chavin KD. Multiple-dose administration of Ginkgo biloba did not affect cytochrome P-450 2D6 or 3A4 activity in normal

46) volunteers. J Clin Psychopharmacol. 2003;23:576-581.

47) Mathhews MK Jr. Association of ginkgo biloba with intracerebral haemorrhage. Neurology. 1998;50:1933-1934.

48) Mohutsky MA, Anderson GD, Miller JW, Elmer GW. Ginkgo biloba: evaluation of CYP2C9 drug interactions in vitro and in vivo. Am J Ther. 2006;13:24-31.

49) Morris J, Burke V, Mori TA, Vandongen R, Beilin LJ. Effects of garlic extract on platelet aggregation: a randomized placebo-controlled double-blind study. Clin Exp Pharmacol Physiol. 1995;22:414-417.