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## HERB-DRUG INTERACTIONS: AN OVERVIEW OF MECHANISMS AND CLINICAL ASPECTS

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**ABSTRACT:** 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 phytochemicals 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 herb-drug interactions will make health care professionals and patients pay more attention to the potential interactions.

**INTRODUCTION:** The term 'Herbal products' has become a colloquial term which 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<sup>1</sup>. 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<sup>2</sup>. According to WHO estimates, demand for medicinal plants by the year 2050 would be ~US \$5 trillion<sup>3</sup>.

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

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often underestimated<sup>4</sup> 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
- Presence of multiple components of various pharmacological properties in the herbs
- Lack of data on the pharmacological action and mechanisms of interactions of herbal products<sup>4</sup>
- Misinformation on the actual label content of herbal products<sup>4,5</sup>
- Low potential of herb induced adverse effects

Furthermore, 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<sup>6,7</sup>. 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:

Knowledge of the mechanism by which a given herb-drug interaction occurs is often clinically 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 of drugs which results in altered levels of the drug or its metabolites.

### 2.1.1 Herb-drug interactions at absorption level

#### 2.1.1.1 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<sup>8</sup>. 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<sup>9</sup>. ABC transporters are relatively easily modulated by factors such as therapeutic drugs and herbal medicines, foods and beverages<sup>10</sup>.

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 non-competitive 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<sup>11</sup>.

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

#### (i) P- Glyco protein (P-gp):

P-gp is also known as multi-drug resistance protein 1 (MDR1) or ABC subfamily B, member 1<sup>12</sup>. P-Glycoprotein 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<sup>12</sup>. P-gp 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 non-competitive 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<sup>7</sup>. 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<sup>13</sup>.

❖ **Some examples of herb drug interactions 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)<sup>14</sup>.
- *Citrus paradisi* (Grapefruit juice) was found to inhibit P-gp rhodamine-123 efflux *in vitro* in Caco-2 cells<sup>15</sup> and *in vivo* in healthy volunteers<sup>16</sup>. It was also found to increase the bioavailability of nifedipine *in vivo* in rats<sup>17</sup> and talinolol *in vitro* in Caco-2 cells<sup>18</sup>.
- 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<sup>19</sup>. The diallyl sulphide which is an active constituent in garlic can also induce P-gp and MRP2 expression *in vitro*<sup>20</sup>. Interestingly, diallyl trisulfide has been shown to inhibit the activity and expression of P-gp in a recent study<sup>21</sup>.
- *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<sup>22</sup>. 6-gingerol

inhibited P-gp-mediated efflux of daunorubicin and rhodamine-123 in KB-C2 cells<sup>23</sup>. The *in vitro* or *in vivo* activity of human P-gp was significantly reduced by *Ginkgo biloba* (ginkgo) extract<sup>8</sup>.

**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<sup>11</sup>. 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<sup>11</sup>. 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<sup>12</sup>. MRP2 is also responsible for the biliary secretion of organic anions such as acetaminophen glucuronide and camptothecin<sup>24</sup>.

**(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'<sup>25</sup>. 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<sup>26</sup>. BCRP confers resistance to a narrower range of anticancer agents than P-glycoprotein and MRP.

### ❖ Some examples of herb drug interactions 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*<sup>27</sup>. 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<sup>28</sup>. On the other hand, BCRP does not confer resistance to the *Vinca* alkaloids, epipodophyllotoxins, paclitaxel, or cisplatin<sup>29</sup>.

### (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:

- 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<sup>30, 31</sup>. 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<sup>32</sup>.

- Inhibition of OATP1 and OATP3 by components of *Citrus sinensis* (Seville orange) and *Malus domestica* (apple) juices may decrease drug uptake and lead to sub-therapeutic drug concentrations *in vitro* and *in vivo*<sup>33</sup>. On the other hand, Takano *et al.* suggest that over-induction of OATP may increase drug uptake and lead to toxic blood drug concentrations<sup>11</sup>.

### 2.1.1.2 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*<sup>34, 35</sup>. *Echinacea purpurea* and *Hypericum perforatum* which are known to induce diarrhoea as side effects may also affect drug absorption in a similar manner<sup>35</sup>. 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.

### 2.1.1.3 Herb interactions through complex formation:

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:

- 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<sup>36</sup>. For instance, the absorption of iron from an iron-fortified meal was significantly reduced by *Capsicum annum*<sup>37</sup>. 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<sup>38</sup>. 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 (*Hypericum perforatum*) induces CYP3A4 and CYP2B6, resulting in a decrease in plasma levels of irinotecan and imatinib, which are two chemotherapeutic drugs<sup>39, 40</sup>. Hyperforin, a major active ingredient of St. John's wort, is the agonist of PXR which can modulate CYP3A4 expression<sup>41</sup>. In mouse, the administration of garlic juice for 8 days induced the protein expression of CYP1A2 and 2E1<sup>42</sup>. In human, the *in vivo* activity of CYP3A4 was increased, by ginkgo extract<sup>43</sup>.

### ❖ 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<sup>44, 45</sup>.
- Garlic extract inhibited *in vitro* CYP2C9, 2CY2C19, CYP3A4, 3A5, and 3A7 activity, while it did not affect the CYP2D6 activity, and increased the activity in recombinant human CYP isozyme system<sup>20</sup>.

- 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<sup>43</sup>.
- Ginger extract inhibited CYP2C9 and 3A4 activities in recombinant human CYP isozyme system<sup>46</sup> and CYP2C19 activity in human liver microsomes<sup>47</sup>.

### 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<sup>48</sup>.

### 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<sup>48</sup>. 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<sup>49</sup>.

- 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 hepatotoxic<sup>78</sup>. *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<sup>50</sup>.

### 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<sup>51</sup>.

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 co-administered drugs through simultaneous effects on the same drug targets<sup>52</sup>. 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<sup>53</sup>. 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<sup>54</sup>.

### 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<sup>55</sup>.

- 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<sup>56</sup>. 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<sup>57</sup>. Garlic preparations decrease the plasma concentrations of saquinavir<sup>58</sup>. 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<sup>53</sup>.

- 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 life-threatening. 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 inter-individual differences in the expression, activity of drug metabolizing enzymes and transporters, co-medication with other drugs, age and many of other physiopathological factors.

- There are several reports where ginseng induced mania when used concomitantly with phenelzine<sup>59</sup> and ginkgo raised blood pressure when combined with a thiazide diuretic<sup>60</sup> and

caused coma when combined with trazodone, an atypical antidepressant<sup>60</sup>.

- Enhanced anticoagulation and bleeding was observed when patients on chronic warfarin therapy consumed danshen (*S. miltiorrhiza*)<sup>61</sup>.
- Kava (*Piper methysticum*) caused a semicomatose state when given concomitantly with alprazolam<sup>62</sup>. A patient with Parkinson's disease taking levodopa in combination with kava had increased duration and number of "off" periods<sup>63</sup>. 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<sup>64</sup>.

#### 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<sup>65</sup>. 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 Interactions:

**Beneficial effects:** 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<sup>66</sup>. 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<sup>33</sup>.

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<sup>67</sup>. 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<sup>68</sup>.

*Centella asiatica* can also be used as an adjunctive medication for patients with epilepsy due to its additive anticonvulsant activity<sup>69</sup>. *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<sup>70</sup>. 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 patient compliance<sup>71</sup>.

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<sup>72</sup>. Further, studies also prove that Rosemary (*Rosmarinus officinalis*) has chemopreventive effect as it increases efflux and intracellular accumulation of doxorubicin and vinblastine<sup>73</sup>. *In vitro* studies also revealed that



silybinin enhances the antitumour activity of cisplatin<sup>74</sup>. 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:** There is a continued global increase in the use of herbal products and supplements which has led to notable increase in the incidence of herb – drug interactions. Herbs may interact with drugs either by pharmacokinetic or pharmacodynamic mechanisms. Pharmacokinetic interactions involve different mechanisms that influence the absorption, metabolism, distribution and elimination of drugs. Any new drugs that are substrates for CYP3A4 and/or Pgp have a potential to cause herb-drug interactions. When there is an increasing use of herbal medicines by patients worldwide, clinicians should have a better knowledge on herb-drug interactions and adopt proper strategies to minimize harmful herb-drug interactions. Timely identification of drugs that interact with herbal medicines and the underlying mechanism is important. If these drugs have to be used in combination with the herbs, dose adjustment may be needed and discontinuation of therapy is necessary when toxic drug-herb interactions occur. Both patients and clinicians should be educated on the clinical significance of herb-drug interactions.

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