PHARMACODYNAMIC AND PHARMACOKINETIC INTERACTIONS OF HERBS WITH PRESCRIBED DRUGS: A REVIEW

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ABSTRACT

This article is a recapitulation of the current research on interactions of Garlic, St. John’s Wort, Ginkgo biloba, Black pepper, Kava-Kava, Ginseng and Ephedra with a number of prescription and OTC medications. There is extensive use of herbs as herbal medicine or dietary supplements for management of diseases or to enhance immunity. Numerous phytochemical present in herbs alters the enzymatic systems, transporters and/ or the physiological processes resulting into pharmacokinetic and pharmacodynamic interactions with prescribed drugs. Chances of herb interactions will be more for those drugs with narrow therapeutic index and in case of geriatric patients having chronic disorders or those having week immune system. Herbal-drug interactions can be examined by conducting in vitro and in vivo experimental research or by referring published case reports. Herbal interactions should be properly monitored and reported. Monitoring of herbal interactions should be done within a pharmacovigilance network.

Keywords: Herb-drug interactions, St John wort, Kava kava, Ginkgo biloba

Introduction

Around 75-80% of the world population utilizes herbs as herbal medications or dietary complements for cure or management of disease or to enhance immunity (Hooda, 2016). Most of the people consume it with a faith that all herbs are safe and devoid of side effects. When drugs and herbs or certain food are taken together, these may interact in such a way so as to reduce the efficacy of the administered drug or may affect the absorption of nutrients present in food. Both drugs and herbs travel through the digestive tract and may interact leading into serious side reactions. Herbs are often taken together with various therapeutic drugs thereby increasing the chances of Herb-Drug Interactions (Hooda, 2016). It is estimated that around 4 billion people (about 80% world population) for the treatment and prevention of various chronic diseases depend on Herbal Medicinal Products (Ekor, 2013). Herb-Drug Interactions are interactions that occur on co administration of herbal medicinal products and western drugs (Alissa, 2014; Brantley et al., 2014). Herb-drug interactions can be more prominent than drug-drug interactions as herbs contain numerous therapeutically active ingredients. Interactions usually occur between over the counter (OTC) drugs, prescription drugs and various dietary supplements that interact with small food particles and lead to such challenges. Herbal medicines with prescription drugs interfere with metabolic break down of the drug and results in obstruction of desired therapeutic effect. Herbal drug interactions usually involve a phytoconstituent that alters the Minimum Effective Concentration (MEC) level of drug in the blood (Rosenkranz et al., 2012). Geriatric patients (taking three or more medications in chronic situation) and patients affected from diabetes, hypertension and depression are at more risk and should be monitored for such herb-drug interactions (Tachjian et al., 2010; Gupta et al., 2017). Whenever any interaction between herb / dietary supplement and drug occurs, it involves either pharmacokinetic or pharmacodynamic mechanisms.

Pharmacokinetic Interactions: In this, herbal drug alters the ADME i.e. absorption, distribution, metabolism, protein binding or excretion of drugs resulting into alteration in the level of drug or its metabolites (Pasi, 2013; Mamindla et al., 2016). Current evidences report that most of the herbal drug interactions are correlated to oxidative metabolism by (CYP) cytochrome P450 system and by the influence of an herb on the efflux drug transporter P-glycoproteins (P-gp) (Izzo, 2005).

Pharmacodynamic Interactions: These are pertaining to the pharmacological activity of the interactive agents, and may affect organ system, receptor site or enzymes. Pharmacodynamic interactions may be additive (or synergistic), i.e., the herbal medicines improve the pharmacological / toxicological actions of synthetic drugs or antagonistic, i.e., the herbal medicine lessens the effectiveness of synthetic drugs. Interactions of warfarin are established illustration of such type of interactions (Holbrook et al., 2005). Elevated anticoagulant effect could be anticipated when warfarin is administered with anticoagulant herbs/ or with antiplatelet herbs like Garlic, Ginger, Ginkgo biloba etc.

Recent Literature data and surveys suggest that increasing use of Herbal medicinal products with prescribed
Drugs have raised issues related to quality, safety and efficacy of these products and may lead to life-threatening adverse effects. Moreover, amongst patients taking prescription medicines in US, 16% adopted herbal drugs as well (WHO, 2003). There has been widespread use of herbs such as St. John’s Wort, Black pepper, Garlic, Ginkgo biloba, Ginseng, Ephedra and Kava-Kava in the form of dietary supplement for the management of various disorders. Previous reports have shown that that some of herbs such as St John’s wort, Garlic, Ginseng, and Gingko, have given rise to clinical interactions when co-administered with prescription drugs. This review compiles all possible interaction of St John’s Wort, Black pepper, Garlic, Ginseng, and Gingko, and Kava-Kava with a number of prescription and OTC drugs.

(1) John’s Wort (SJW)

Hypericum perforatum, herbaceous perennial plant is native to Europe belonging to Hypericaceae family. Extracts of this plant have been used since ancient times for its efficacy against health ailments (Wheatley, 1998). In Europe and US, SJW is available as OTC product in the form of herbal preparations. It is applied externally for treatment of wounds and burns, or taken in form of herbal drink such as tea to treat fevers and nervous conditions like depression (Wheatley, 1998). Main constituents of SJW includes phenylpropanes, flavonol glycoside (hyperoside), biflavonones, tannins, xanthones, phloroglucinol derivative (hyperforin), naphthodianthrene (hypercin), amino acids and essential oil (Shrivastava and Dwivedi, 2015). Clinical reports revealed that SJW may cause both pharmacokinetic and pharmacodynamic interactions (Izzo, 2004). Pharmacodynamic interactions may occur when SJW is given together with drugs that enhance 5-HT signalling in the brain (e.g. selective serotonin reuptake inhibitors and serotonin (5-HT1) receptor agonist such as triptans used to treat migraine). Pharmacokinetic interactions have been known with drugs like warfarin, oral contraceptives, HIV protease inhibitors, digoxin and cyclosporine. Such types of interactions occur may be due to induction of cytochrome P450 isoenzymes CYP3A4, CYP2C9, CYP1A2 and the transport protein P-gp resulting in decrease in concentration or effect of these prescribed drugs (Zhou et al., 2004). Induction of cytochrome enzymes and P-gp is triggered by hyperforin through activation of the pregnane X receptor. SJW interactions with prescribed drugs are summarised in Table 1.

(2) Black Pepper

Black Pepper is commonly used spices in the world, is dried fruit obtained from Piper nigrum Linn. (Family: Piperaceae). It is widely used as anti-oxidant and enhances absorption of various drugs such as tetracycline and phenytoin (Srinivasan, 2007). It possesses immunomodulatory, antiulcer, antiasthmatic, hepatoprotective and anti-inflammatory functions (Meghwal and Goswami, 2013). It also provides protection against oxidative damage by neutralising the free radicals in cancer patients (Meghwal and Goswami, 2013). It also contains flavonoids, amides, steroids, lignans, and chalcones (Sharon, 2002). Black Pepper or piperine has been stated to improve the bioavailability of therapeutic drugs as well as phytoconstituents by either promoting intestinal absorption or reducing drug metabolism or by the combination of these two (Han, 2011). It increases absorptive surface in small intestine by alteration of membrane dynamics and permeation characteristics (Khajuria et al., 2002). It inhibits enzymes such as UDP-glucuronyl transferase, and hepatic and intestinal aryl hydrocarbon hydroxylase. It also inhibits CYP isoforms like CYP2C9 and CYP3A4. Black Pepper or piperine may affect the P-gp mediated drug efflux via the modulation of functional activity as well as gene expression of P-gp (Bhardwaj et al., 2002). It may produce the dose dependent increase in gastric acid secretion and delay gut motility. Concomitant use of piperine significantly enhances the intestinal absorption of curcumin and retained the curcumin longer in the tissues (Han, 2011). Piperine significantly enhanced the bioavailability of (-)-epigallocatechin-3-gallate (EGCG), the polyphenols from green tea (Camellia sinensis) (Lambert et al., 2004). Interactions of Black Pepper or Piperine with prescribed drugs are summarised in Table 2.

(3) Garlic

Garlic (Allium sativum Linn., family Alliaceae) is cultivated extensively in Central Asia, Siberia and West of the Himalayas. It is a perennial bulb which is used to impart flavor and aroma in food (Tattelman, 2005). Greek physician Hippocrates and Galen used this herb for the treatment of intestinal disorders. Use of garlic in weakness, cough, skin diseases, rheumatism, and haemorrhoids were mentioned in the Vedas (Petrovska and Cekovska, 2010). Garlic contains sulphur-based compounds called Alliin which is odorless chemical derived from the amino acid cysteine. It is further converted into allicin and finally into ajoene, strongly smelling compound. The ajoene has ability to prevent formation of clots in blood vessels and treatment of atherosclerosis (Lawson and Wang, 2005). It also contains peptides, terpenoids, flavonoids, phenol derivatives and various enzymes in minute proportions along with protein, fat, crude fibre, potassium, iron, magnesium etc (Odebunmi et al., 2009). Garlic is useful in skin diseases, arthritis, lumbago, backache, chronic fever, malaria, tuberculosis, urinary diseases, diabetes, kidney stones, anaemia, epilepsy, etc. Allicin and other compounds possess antihypertensive, hypolipidaemic, hypocholesterolemic and antiinflammatory effects. Sulphur compounds in Garlic also have anticarcinogenic properties. These also prevent arteriosclerosis (Chan et al., 2013). Interaction of Garlic with antihypertensives and antiabetic drugs is mostly pharmacodynamic whereas that with anticoagulants, antivirals and antitubercular is pharmacokinetic (Table 3). Garlic competitively inhibits the activity of CYP3A4, CYP2C9 and CYP2C19 in drug metabolism. Pgp and multidrug resistance associated protein-2 (MRP-2) are also found to be activated by garlic and its components. Decreased activity of CYP3A4 and induction of P-gp by Garlic is responsible for increased clearance and decreased bioavailability of drugs. Organosulfur components of garlic, on the other hand, increase the expressions of CYP1A1, CYP2B1 and CYP3A1 (Adhikari et al., 2015).

(4) Ginkgo biloba

Ginkgo biloba (family Ginkgoaceae), or Maidenhair is one of the most frequently available OTC herbal medicinal product in Germany and United states (Diamond et al., 2000). Gingko seeds and extract play a vital role in the TCM...
(Traditional Chinese Medicines) and are widely illustrated as popular dietary supplements in Europe (DeKosky et al., 2008). It is used to treat anxiety, dementia and other vascular disorders especially alzheimer disease (Ihl et al., 2011). It also has the ability to improve blood circulation and improves psychomotor function (Ponto and Schultz, 2003). It is also used in Schizophrenic patients as an adjunct therapy to antipsychotic drugs (Chen et al., 2015). Gingko biloba contains a wide number of phytoconstituents such as alkylphenols (ginkgolic acids), flavonoids (bilobetin, ginkgetin, quercetin, etc.) and terpenoids (bilobalides, ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide J, etc.) and organic acids (6-hydroxykynurenic acid, protocatechuic acid, p-hydroxybenzoic acid, ferulic acid, clorigenic acid, etc) (Singh et al., 2008; Liao et al., 2011). Gingkoglide (mainly ginkgolide B) are potent inhibitors of PAF-induced thrombocytopenia and constriction of bronchioles (Xin et al., 2015). G. biloba extracts and their constituents are inhibitors and inducers of drug-metabolizing CYP enzymes and transporters (Unger, 2013). Ginkgo leaves also contains ginkgotoxin, a B6 antivitamin which may cause epileptic seizures and other severe neuronal disorders, even death (Kajiyama et al., 2002). Interactions of G. biloba with drugs are summarised in Table 4.

(5) Ginseng

Ginseng is amongst the most popular herbal medicinal plant used as immunomodulator in countries including Korea, Japan and China (Wang et al., 2015). Among various ginseng species, Asian ginseng (Panax ginseng) and American ginseng (Panax quinquefolium), family Araliaceae are the most widely used species. Ginseng has been used to improve concentration, counteract alzheimer disease; increases work efficiency and stamina with better well being (Wang et al., 2012). It also has the ability to stimulate CNS to modulate immune system and anabolic effects, thus also known as immunomodulator or adaptogen (Nocerino et al., 2000). Ginseng is known to have varied pharmacological actions such as antifatigue, antiaging, antidiabetic, anticancer (Attele et al., 1999; Yuan et al., 2012). Various classes of constituents present in ginseng are saponin glycosides (ginsenosides or panaxosides derivative of aglycone-protopanaxadiol, protopanaxatriol and oleanolic acid); polysaccharides (water soluble and include panaxane A to U); Polynes (Panaxynol , panaxytriol) and Volatile oil (α-bisabolol, thujopsene, α-cadinol) (Christensen, 2008). Naturally occurring ginsenosides may affect hepatic P450 activities of CYP2A6, CYP2C9 and CYP3A4 (Liu et al., 2006; Kim et al., 2016). Ginseng extract also inhibited CYP1A1, 1A2, and 1B1 activities in recombinant human CYP isozyme system (Chang et al., 2002). Clinical pharmacokinetic studies in humans revealed that interactions of P. ginseng with drugs appear to be rare but still close monitoring is advised for patients consuming CYP3A or P-gp substrates with narrow therapeutic indices (Ramanathan and Penzak, 2017). Table 5 summarizes case studies of potentially serious interactions of Ginseng with warfarin, imatinib, etc.

(6) Ephedra

Ephedra (Ma-Huang) consist of dried young aerial stem of Ephedra species such as E. equisetina, E. gerardina, E. sinica etc. belonging to the family Gnetaceae (Ephedraceae). It is one of the oldest herbs which is beneficial to mankind for thousand years and originally belongs to Traditional Chinese Medicine (TCM) system (Caveney et al., 2001). Ephedrine and Pseudoephedrine are the major alkaloids that were reported in Ephedra species. Ephedrine was first isolated by Japanese Chemist Nagai in 1887 and major constituent comprising 30-90% of the alkaloids (González-Juárez et al., 2020). Other amino alkaloids present in ephedra include methylephedrine, norephedrine, methypseudoephedrine etc. (Gurley et al., 1998). The drug also contains bioactive compound oxalidone derivative (ephedroxane) (Konno et al., 1979). Other constituents present in Ephedra include flavones, flavanols, tannins and carboxylic acids (Ibragic and Sofic, 2015). Ephedra is used as bronchodilator, for weight loss in obesity, and to boost performance of athletes. Ephedrine is known to stimulate thermogenesis in adipose tissues (boost the fat burning process in body). It is also used in hay fever and allergies. Ephedrine stimulates the heart, lungs and nervous system. It is sympathomimetic amine causes an indirect stimulation of adrenergic receptors by enhancing the action of nor-epinephrine at the post synaptic α and β receptors. L-ephedrine and nor-pseudoephedrine has an ability to cross the blood brain barrier and therefore used as CNS stimulant related to amphetamines. Ephedrine increases resting metabolic rate means the number of calories your body burns at rest. (White et al., 1997; Limberger et al., 2013).

Ephedrine activates adrenergic receptors and can enhance heart beat and peripheral vascular resistance. It can also act on the CNS giving the individual a sensation of tremendous well-being (Manoor, 2001). Ephedra increases blood pressure, risk of heart attack, seizures, stroke, irregular heartbeat, kidney stones, restlessness, anxiety, and etc (Abourashed et al., 2003). There may be enhanced risk of interactions of Ephedra supplements in persons with hypertension and heart disease. A 2003 analysis published in Neurology also established that ephedra-containing products increased risk of stroke (Karch, 2003). Table 6 summarizes reports of potentially serious interactions of Ephedra with various drugs. In June 1997, FDA purposed restriction on Ephedrine content of Dietary supplements due to the adverse interactions reported. On December 30, 2003 the US FDA issued ban of supplements containing ephedra in the U.S for the first time since passage of DSHEA Act, 1994 (Haller and Benowitz, 2000; Blanck et al., 2001; Rados, 2004). Countries like Canada also supported the purposed restrictions on Ephedrine content and recalled products that contained more than the recommended dose (Sibbald, 2002).

(7) Kava

Kava Kava consist of dried rhizome of the plant Piper methysticum belonging to family Piperaceae. The plant is native to islands of Pacific Ocean and is traditionally used in the South Pacific as a popular social drink (Anke et al., 2006). It was first cultivated about thousand years ago and in traditional documents it is used both as a medicine and a beverage. Today, it is mostly used as an effective herbal anxiolytic (Pittler and Ernst 2000). It is also used to potentiate the well being of an individual by relieving stress and restlessness (Sarris et al., 2011). It also possesses antiepileptic and antipsychotic action. It is also used for the treatment of migraine and depression disorders (Schulz et al., 2004). Kava contains pharmacologically active constituents
such as kavalactones (or kavapyrones) which include kavain, dihydrokavain, methysticin, dihydromethysticin, desmethoxyyangonin and yangonin (Ramzan and Tran 2004; Teschke et al., 2011). Apart from lipophilic compounds kavalactones, it also contains alkaloids and flavonoids. In 1998, various adverse effects of hepatotoxicity were reported with kava-based products and this led to its ban in many countries such as Germany, France, Australia and Canada (Lim et al., 2007). However, in 2002, Kava containing products continued to be sold in U.S. but the FDA warned the customers that these kava containing dietary supplements can cause severe liver damage (Teschke and Schulze, 2010). Kava has a more potential for causing pharmacokinetic drug interaction, as kavalactones present in Kava extract are potent inhibitors of several enzymes of CYP450 system (CYP1A2, CYP2C9, CYP2C19 and CYP3A4) (Mathews et al., 2004). Crude extract and the kavalactones of P. methysticum also showed in vitro P-gp inhibitory activity (Weiss et al., 2005). Pharmacodynamic interactions of Kava have been reported with CNS depressant and anticonvulsant drugs (Table 7). Kavalactones potentiates the effect of CNS depressants like benzodiazepines, barbiturates and alcohol.

**Conclusion**

It is a general notion that herbal drugs are safe and can be taken with prescribed synthetic drugs without consultation of clinical pharmacist and physician. Generally, people take household therapy (herbal products) along with medicines prescribed by physician to manage their chronic diseases, e.g., diabetic patients on oral sulphfonylurea derivatives usually take Karela juice or ginseng without knowing the fact that such combination of herbal drugs with synthetic medicines may lead to excessive hypoglycaemia because of synergistic or additive interactions. Herbal drugs are complex mixture of chemical constituents which may interact with prescribed drugs and modify pharmacokinetic or pharmacodynamic profile of drugs leading to change in therapeutic efficacy and safety. The present review has been compiled with an objective to help patients, clinical pharmacists and physicians to select appropriate medication (combination of herbal product and prescribed drug) so that herbal drug interactions can be avoided.

**Table 1: Interactions of St John’s Wort (SJW) with Prescribed Drugs**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drugs</th>
<th>Potential effect</th>
<th>Possible Mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>With cyclosporin, tacrolimus (immunosuppressant drug)</td>
<td>It reduces blood concentration with the risk of organ transplant rejection.</td>
<td>stimulation of CYP3A4 and P-gp substrate.</td>
<td>(Alschler and Klotz, 2003; Mai et al., 2003)</td>
</tr>
<tr>
<td>2</td>
<td>With tibolone, northindrone (oral contraceptive pills)</td>
<td>Decreased blood concentration with chances of unintended pregnancy and breakthrough bleeding.</td>
<td>Induction of CYP3A4.</td>
<td>(Schwarz et al., 2003; Murphy et al., 2005)</td>
</tr>
<tr>
<td>3</td>
<td>With warfarin (anticoagulant drug)</td>
<td>Reduces anticoagulant effect and decreases plasma drug concentration level.</td>
<td>Induction of predominantly CYP2C9A.</td>
<td>(O’Reilly, 1974; Jiang et al., 2004)</td>
</tr>
<tr>
<td>4</td>
<td>With simvastatin, atorvastatin (antihyperlipidemic drugs)</td>
<td>Decreased plasma levels of drug and reduced efficacy of drug in hypercholesterolemia patients.</td>
<td>Induction of CYP3A4 and P-glycoprotein substrate.</td>
<td>(Andrén et al., 2007; Sugimoto et al., 2001)</td>
</tr>
<tr>
<td>5</td>
<td>With Nifedipine, Verapamil (calcium channel blockers)</td>
<td>Decreased the AUC of drug and decreased efficacy.</td>
<td>Induction of CYP3A4 through first-pass metabolism.</td>
<td>(Tannergren et al., 2004; Wang et al., 2009)</td>
</tr>
<tr>
<td>6</td>
<td>With digoxin</td>
<td>Reduced the Plasma Drug Concentration level and increased cases of Loss of Autorhythmicity.</td>
<td>Induction of P-gp resulting in reduced blood concentration of digoxin</td>
<td>(Mueller et al., 2004)</td>
</tr>
<tr>
<td>7</td>
<td>With indinavir, lamivudine, nevirapine (anti-HIV drugs)</td>
<td>The drug becomes totally ineffective and resulted in increased clearance.</td>
<td>Induction of P-glycoprotein substrate and nevirapine is metabolised by CYP3A4 &amp; CYP2B6.</td>
<td>(Erickson et al., 1999; De Maat et al., 2001)</td>
</tr>
<tr>
<td>8</td>
<td>With irinotecan, imatinib (anti-Cancer drugs)</td>
<td>Reduced plasma Drug concentration level and increased drug clearance.</td>
<td>CYP3A4 and P-gp induction.</td>
<td>(Frye et al., 2004; Smith et al., 2004)</td>
</tr>
<tr>
<td>9</td>
<td>With alprazolam, midazolam (benzodiazepines)</td>
<td>Reduced plasma drug concentration level and decreased efficacy of drug in healthy volunteers.</td>
<td>Induction of CYP3A4 activity.</td>
<td>(Markowitz et al., 2003)</td>
</tr>
<tr>
<td>10</td>
<td>With mefenytoin, carbamazepine (antiepileptic drugs)</td>
<td>Reduced plasma drug concentration level with risk of seizures.</td>
<td>Induction of CYP3A4 activity and CYP2C8</td>
<td>(Kerr et al., 1994; Johne et al., 2004)</td>
</tr>
</tbody>
</table>
11. With tolbutamide, gliclazide (hypoglycemic drugs) | Reduced plasma drug concentration level with reduced efficacy of drugs in type-II diabetes patients. | Induction of CYP2C9 substrate genotype. | (Xu et al., 2008)

12. With theophylline, fexofenadine (drugs acting on the respiratory system) | Decreased Plasma levels of the drug with increased cases of chronic airway constriction. | Induction of CYP1A2 and CYP3A4 in case of theophylline and P-glycoprotein in case of fexofenadine. | (Nebel et al., 1999; Dresser et al., 2003)

13. With citalopram, fluvoxamine, sertraline (selective serotonin reuptake inhibitors) | Concomitant use results in serotonin syndrome that leads to confusion, fever, tremor, nausea etc. | Enhanced serotonin concentration | (Hammerness et al., 2003; Haller, 2006)

14. With triptans (sumatriptan, naratriptan, raizatriptan) | Co administration leads to increased serotonergic effect with adverse effects. | Potentiate serotonin concentration | (Ohnishi and Yokoyama, 2004; Yang et al., 2006a)

### Table 2: Interactions of Black pepper with Prescribed Drugs

<table>
<thead>
<tr>
<th>S. No.</th>
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<th>Potential effect</th>
<th>Possible Mechanism</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>With phenytoin, carbamazepine (antiepileptic drugs)</td>
<td>Enhances plasma drug concentration level and increases the oral bioavailability of the drug</td>
<td>Inhibition of CYP3A4.</td>
<td>(Pattanaik et al., 2009)</td>
</tr>
<tr>
<td>2.</td>
<td>With theophylline, fexofenadine (drugs acting on the respiratory system)</td>
<td>Increased plasma drug concentration and oral bioavailability of drug</td>
<td>Inhibition of P-glycoprotein.</td>
<td>(Jin and Han, 2010)</td>
</tr>
<tr>
<td>3.</td>
<td>With ampicillin trihydrate, cefotaxime sodium (β-Lactam antibiotics)</td>
<td>Increased bioavailability of the drug in oral formulations</td>
<td></td>
<td>(Hiwale et al., 2002; Janakiraman and Manavalan, 2011)</td>
</tr>
<tr>
<td>4.</td>
<td>With indinavir, lamivudine, nevirapine (anti-HIV drugs)</td>
<td>Increases plasma drug concentration level and the drug become more efficacious.</td>
<td></td>
<td>(Kasibhatta and Naidu, 2007)</td>
</tr>
<tr>
<td>5.</td>
<td>With metronidazole</td>
<td>Increased plasma drug concentration level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>With diclofenac sodium and pentazocine (analgesics)</td>
<td>The analgesic activity of the drug increases due to enhanced absorption and reduced elimination</td>
<td></td>
<td>(Pooja, 2007)</td>
</tr>
<tr>
<td>7.</td>
<td>With omeprazole (a proton pump inhibitor)</td>
<td>Significant increase in oral bioavailability of the drug with increased efficacy.</td>
<td></td>
<td>(Boddupalli et al., 2014)</td>
</tr>
<tr>
<td>8.</td>
<td>With pentobarbitone</td>
<td>Piperine potentiated the sleeping time caused by the drug.</td>
<td>Inhibition of liver microsomal enzymes.</td>
<td>(Mujumdar et al., 1990)</td>
</tr>
<tr>
<td>9.</td>
<td>With Cyclosporine</td>
<td>Piperine increases the level of cyclosporine in the body</td>
<td>Inhibition of the drug transporter P-gp</td>
<td>(Bhardwaj et al., 2002)</td>
</tr>
<tr>
<td>10.</td>
<td>With digoxin</td>
<td>Piperine increases the level of digoxin in the body</td>
<td>Inhibition of the drug transporter P-gp</td>
<td>(Bhardwaj et al., 2002)</td>
</tr>
<tr>
<td>11.</td>
<td>With propranolol, atenolol (antihypertensive drugs)</td>
<td>Enhanced oral bioavailability of the drug with increased efficacy.</td>
<td></td>
<td>(Bano et al., 1991; Singh and Chand, 2011)</td>
</tr>
<tr>
<td>13.</td>
<td>With glimepride (hypoglycemic drug)</td>
<td>Enhanced bioavailability and improved antidiabetic effect.</td>
<td>Inhibition of CYP2C9 activity.</td>
<td>(Veeresham et al., 2012)</td>
</tr>
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</table>
### Table 3: Interactions of Garlic with Prescribed Drugs

<table>
<thead>
<tr>
<th>S. No.</th>
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<th>Potential effect</th>
<th>Possible Mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>With warfarin (anticoagulant drug)</td>
<td>Garlic inhibits platelet function and increases the bleeding risk</td>
<td>Inhibits CYP3A4 and effects the plasma concentration of warfarin.</td>
<td>(Bordia, 1978; Rahman and Billington, 2000)</td>
</tr>
<tr>
<td>2.</td>
<td>With saquinavir (antiviral drug)</td>
<td>Reduced oral bioavailability of the drug due to Increased Clearance.</td>
<td>Inhibition of CYP3A4 and Induction of P-gp.</td>
<td>(Piscitelli et al., 2002)</td>
</tr>
<tr>
<td>3.</td>
<td>With chlorozoxazone (skeletal muscle relaxant)</td>
<td>Enhanced plasma drug concentration level due to decreased metabolism.</td>
<td>Inhibition of CYP2E1 enzyme.</td>
<td>(Gurley et al., 2005; Shi and Klotz, 2012)</td>
</tr>
<tr>
<td>4.</td>
<td>With atorvastatin (antihyperlipidemic drug)</td>
<td>Enhances the plasma concentration of drug leading to increased lipid peroxidation which will damage the kidney thereby increases the risk of nephrotoxicity.</td>
<td>Inhibition of CYP3A4</td>
<td>(Reddy et al., 2012)</td>
</tr>
<tr>
<td>5.</td>
<td>With isoniazid (antitubercular agent)</td>
<td>Reduced oral bioavailability and decreased the efficacy of the drug</td>
<td></td>
<td>(Dhamija et al., 2006)</td>
</tr>
<tr>
<td>6.</td>
<td>With docetaxel (antineoplastic drug)</td>
<td>Enhanced plasma drug concentration level due to reduced clearance</td>
<td></td>
<td>(Yang et al., 2010)</td>
</tr>
<tr>
<td>7.</td>
<td>With glibenclamide (antidiabetic Drug)</td>
<td>Increased hypoglycemic effect</td>
<td>Pharmacodynamic interaction</td>
<td>(Poonam et al., 2013)</td>
</tr>
<tr>
<td>8.</td>
<td>With hydrochlorothiazide etc (diuretics)</td>
<td>Enhanced oral bioavailability due to decreased clearance.</td>
<td>Inhibition of CYP3A4 Substates</td>
<td>(Asdaq and Inamdar, 2009)</td>
</tr>
<tr>
<td>9.</td>
<td>With atenolol (β-blocker)</td>
<td>Garlic interacts with atenolol resulting in reduced serum LDH and CK-MB activity (an increase of CK-MB is found in hypertensive patient)</td>
<td>Synergistic action/Pharmacodynamic interaction</td>
<td>(Avula et al., 2014)</td>
</tr>
<tr>
<td>10.</td>
<td>With Propranolol (β-blocker)</td>
<td>Synergistic antihypertensive action</td>
<td>Pharmacodynamic interaction</td>
<td>(Asdaq and Inamdar, 2010)</td>
</tr>
<tr>
<td>11.</td>
<td>With captopril (ACE inhibitor)</td>
<td>Synergistic antihypertensive and cardio-protective effect</td>
<td>Pharmacodynamic interaction</td>
<td>(Asdaq and Inamdar, 2010)</td>
</tr>
</tbody>
</table>

### Table 4: Interactions of G. biloba with Prescribed Drugs

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drugs</th>
<th>Potential effect</th>
<th>Possible Mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>With NSAIDs</td>
<td>Spontaneous bleeding, may cause fatal intracerebral haemorrhage</td>
<td>Ginkgo reduces aggregation of platelet by rising concentrations of endothelium-derived thrombolitics</td>
<td>(Diamond et al., 2000; Bent et al., 2005)</td>
</tr>
<tr>
<td>2.</td>
<td>With nifedipine (calcium channel blocker)</td>
<td>Reduced hypotensive action</td>
<td>Induction CYP3A</td>
<td>(Yoshioka et al., 2004)</td>
</tr>
<tr>
<td>3.</td>
<td>With ritonavir (antiviral Drugs)</td>
<td>Decreased AUC due to reduced oral bioavailability of the drug.</td>
<td>Not known</td>
<td>(Robertson et al., 2008; Izzo and Ernst, 2009)</td>
</tr>
<tr>
<td>4.</td>
<td>With omeprazole (A proton Pump Inhibitor)</td>
<td>Reduced plasma drug concentration level due to increased clearance.</td>
<td>Induction CYP2C19</td>
<td>(Yin et al., 2004)</td>
</tr>
<tr>
<td>5.</td>
<td>With phenytoin, carbamazepine, Valproic acid (antiepileptic drugs)</td>
<td>Ginkgo potentiates seizures and decreases the effectiveness of anticonvulsant drugs such as Phenytoin and valproic acid.</td>
<td>Ginkgo induces the effect of CYP2C9 and CYP2C19 resulting in sub-therapeutic levels of drug.</td>
<td>(Kupiec and Raj, 2005)</td>
</tr>
<tr>
<td>6.</td>
<td>With losartan (first non-peptide angiotensin-II receptor blocker)</td>
<td>Enhanced plasma drug concentration due to reduced metabolism.</td>
<td>Inhibition of CYP450 enzyme system.</td>
<td>(Klishadi et al., 2015; Wang et al., 2016)</td>
</tr>
<tr>
<td>7.</td>
<td>With tolbutamide (hypoglycemic drug)</td>
<td>Enhanced Bioavailability and improved antidiabetic effect</td>
<td>Inhibition of CYP2C9 Activity and P-gp.</td>
<td>(Sugiyama et al., 2004; Uchida et al., 2006)</td>
</tr>
</tbody>
</table>
8. With theophylline
   Decreased Plasma levels of the drug with increased cases of chronic airway constriction
   Induction of CYP1A2 (Tang et al., 2007)

9. With cyclosporine
   Reduced bioavailability
   Inhibition P-gp, induction CYP3A4 (Yang et al., 2006b)

10. With propranolol (β-Sympatholytic drug)
    Decreased plasma concentrations of propranolol
    Induction of CYP1A2 and CYP3A4 enzyme. (Zhao et al., 2006)

11. With fluoxetine and buspirone (SSRIs)
    Hypomania
    Both affects the brain and induced hyper and over excited state. (Spinella and Eaton, 2002)

<table>
<thead>
<tr>
<th>S. No.</th>
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<th>Possible Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>With warfarin (anticoagulant drug)</td>
<td>Reduced anticoagulant effect and decreases plasma drug concentration level as a result bleeding risk also increases.</td>
<td>Induction of CYP450 enzyme system</td>
<td>(Janetzky and Morreale, 1997; Vaes and Chyka, 2000)</td>
</tr>
<tr>
<td>2.</td>
<td>With alcohol</td>
<td>Ginseng relieves the symptoms of alcohol hangover.</td>
<td>Ginseng decreased plasma ethanol concentration by delaying gastric emptying</td>
<td>(Koo, 1999; Lee et al., 2014)</td>
</tr>
<tr>
<td>3.</td>
<td>With phenelzine MAO inhibitor (antidepressant drug)</td>
<td>Concomitant use of Ginseng with phenelzine may cause excess of stimulation leading to side effects like anxiousness, restlessness and insomnia.</td>
<td>Inhibition of cAMP phosphodiesterase and thus increase cAMP level.</td>
<td>(Stancheva and Alova, 1993; Jones and Runikis, 1987)</td>
</tr>
<tr>
<td>4.</td>
<td>With imatinib (anticancer drug)</td>
<td>Hepatotoxicity was observed in 26 years old man with chronic myelogenous leukaemia when ginseng is simultaneously taken with imatinib.</td>
<td>Ginseng may inhibit CYP3A4 concerned in metabolism of Imatinib.</td>
<td>(Bilgi et al., 2010)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S. No.</th>
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<th>Possible Mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>With dexamethasone (steroids)</td>
<td>Co-administration results in poor bioavailability of dexamethasone</td>
<td>Ephedra increases the clearance</td>
<td>(Jubiz and Meikle, 1979; Brooks et al., 1997)</td>
</tr>
<tr>
<td>2.</td>
<td>With theophylline, caffeine (methyl xanthine)</td>
<td>May stimulate insomnia, anxiety and adverse G.I.T effects like vomiting.</td>
<td>Additive neurologic, cardiovascular and psychiatric adverse effect or toxicity</td>
<td>(Weinberger et al., 1975; Tormey and Bruzzi, 2001)</td>
</tr>
<tr>
<td>3.</td>
<td>With phenelzine (MAO inhibitors)</td>
<td>Co-use stimulates the body and might result in synergistic actions such as fast heart beat, seizures, nervousness etc.</td>
<td>MAO inhibitors increase the level of serotonin and Ephedra also stimulates the body by releasing neurotransmitters.</td>
<td>(Dawson et al., 1995)</td>
</tr>
<tr>
<td>4.</td>
<td>With Ergotamine, Bromocryptine (Ergot Derivatives)</td>
<td>Additive effect leads to hypertension thereby such medications should be monitored before prescribing</td>
<td>Synergistic pharmacodynamic interaction</td>
<td>(Martin et al., 1971)</td>
</tr>
<tr>
<td>5.</td>
<td>With cholinergic agents</td>
<td>Hypotension</td>
<td>Antagonistic effect</td>
<td>(Boada et al., 1999)</td>
</tr>
<tr>
<td>6.</td>
<td>With Anaesthetics</td>
<td>Relapse of epidural block</td>
<td>Ephedrine reduces the efficacy of the drug</td>
<td>(Ueda et al., 1995; Kanaya et al., 2002)</td>
</tr>
</tbody>
</table>
Table 7: Interactions of Kava Kava with Prescribed Drugs

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drugs</th>
<th>Potential effect</th>
<th>Possible Mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>With alprazolam (potent anxiolytic benzodiazepine)</td>
<td>Co-use causes excessive drowsiness or disorientations</td>
<td>Additive effect on GABA receptor</td>
<td>(Jamieson et al., 1989; Almeida and Grimsley, 1996)</td>
</tr>
<tr>
<td>2.</td>
<td>With caffeine (Methyl xanthine alkaloid)</td>
<td>Rhabdomyolysis, severe muscular pain</td>
<td>-</td>
<td>(Donadio et al., 2000)</td>
</tr>
<tr>
<td>3.</td>
<td>With chlorzoxazone (skeletal muscle relaxant)</td>
<td>Decreased plasma drug concentration level due to faster clearance rate</td>
<td>Inhibition of CYP2E1</td>
<td>(Izzo and Ernst, 2009)</td>
</tr>
<tr>
<td>4.</td>
<td>With digoxin</td>
<td>No marked effect was observed on pharmacokinetics of digoxin</td>
<td>-</td>
<td>(Gurley et al., 2007)</td>
</tr>
<tr>
<td>5.</td>
<td>With levodopa</td>
<td>Reduced efficacy of levodopa</td>
<td>Kava antagonizes the consequence of dopamine</td>
<td>(Schelosky et al., 1995)</td>
</tr>
<tr>
<td>6.</td>
<td>With alcohol</td>
<td>Concomitant use leads to impaired vigilance or hangover</td>
<td>Synergistic action</td>
<td>(Jamieson and Duffield, 1990; Foo and Lemon, 1997)</td>
</tr>
<tr>
<td>7.</td>
<td>With CNS depressant drugs</td>
<td>Synergistic Sedative effect</td>
<td>GABA Action that results in hyperpolarisation</td>
<td>(Singh and Singh, 2002)</td>
</tr>
<tr>
<td>8.</td>
<td>With anticonvulsants</td>
<td>Lethargy and cognitive impairment.</td>
<td>Synergistic therapeutic effects of kava with anticonvulsants</td>
<td>(Kretzschmar et al., 1970; Schmitz et al., 1995; Spinella, 2001)</td>
</tr>
<tr>
<td>9.</td>
<td>With warfarin and other anticoagulant drugs</td>
<td>Concomitant use might cause excessive bleeding.</td>
<td>Inhibition of CYP3A4</td>
<td>(Gleitz et al., 1997; Spinella, 2001)</td>
</tr>
<tr>
<td>10.</td>
<td>MAO-B inhibitors (Selegiline)</td>
<td>Kavalaactones shows additive effects with Mao-B inhibitors</td>
<td>Pharmacodynamic interaction</td>
<td>(Uebelhack et al., 1998)</td>
</tr>
<tr>
<td>11.</td>
<td>With Acetaminophen and other hepatotoxic drugs</td>
<td>Co-use increases risk of severe liver damage that result in hepatotoxicity</td>
<td>Additive action</td>
<td>(Teschke, 2010; Teschke and Schulze, 2010)</td>
</tr>
</tbody>
</table>

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References


