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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 has 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, *Ginkgo biloba*, Ginseng, Ephedra 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), biflavones, tannins, xanthones, phloroglucinol derivative (hyperforin), napthodianthrone (hypericin), 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: Piperacea). 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). The main active constituent of Black Pepper is piperine (piperidine alkaloid). 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 git 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 antithrombotic effects. Sulphur compounds in Garlic also have anticarcinogenic properties. These also prevent arteriosclerosis (Chan *et al*., 2013). Interaction of Garlic with antihypertensives and antidiabetics 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-hydroxybenzoicacid, ferulic acid, clorgenic acid, etc) (Singh *et al*.,2008; Liao *et al*., 2011). Gingkgolide (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); Polyynes (Panaxynol , panaxytriol) and Volatile oil (α-bisabolol, thujopsene, α-cadinol) (Christensen, 2008). Naturally occurring ginsenosides may affect hepatic P450 activity *in vivo* by means of ginseng's intestinal metabolites. Ginsenoside metabolites are reported to inhibit the enzyme 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 Sofić, 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 (Mansoor, 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*., 2002; Anke and Ramzan 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 sulphonylurea 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

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

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

S. No.	Drugs	Potential effect	Possible Mechanism	References
1.	With phenytoin, carbamazepine (antiepileptic drugs)	Enhances plasma drug concentration level and increases the oral bioavailability of the drug	Inhibition of CYP3A4.	(Pattanaik *et al*., 2009)
2.	With theophylline, fexofenadine (drugs acting on the respiratory system)	Increased plasma drug concentration and oral bioavailability of drug	Inhibition of P-glycoprotein.	(Jin and Han, 2010)
3.	With ampicillin trihydrate, cefotaxime sodium (β-Lactam antibiotics)	Increased bioavailability of the drug in oral formulations		(Hiwale *et al*., 2002; Janakiraman and Manavalan, 2011)
4.	With indinavir, lamivudine, nevirapine (anti-HIV drugs)	Increases plasma drug concentration level and the drug become more efficacious.		(Kasibhatta and Naidu, 2007)
5.	With metronidazole	Increased plasma drug concentration level		(Amar *et al*., 2010)
6.	With diclofenac sodium and pentazocine (analgesics)	The analgesic activity of the drug increases due to enhanced absorption and reduced elimination		(Pooja, 2007)
7.	With omeprazole (a proton pump inhibitor)	Significant increase in oral bioavailability of the drug with increased efficacy.		(Boddupalli *et al*., 2014)
8.	With pentobarbitone	Piperine potentiated the sleeping time caused by the drug.	Inhibition of liver microsomal enzymes.	(Mujumdar *et al*.,1990)
9.	With Cyclosporine	Piperine increases the level of cyclosporine in the body	Inhibition of the drug transporter P-gp	(Bhardwaj *et al*., 2002)
10.	With digoxin	Piperine increases the level of digoxin in the body	Inhibition of the drug transporter P-gp	(Bhardwaj *et al*., 2002)
11.	With propranolol, atenolol (antihypertensive drugs)	Enhanced oral bioavailability of the drug with increased efficacy.		(Bano *et al*.,1991; Singh and Chand, 2011)
12.	With domperidone (prokinetic drug with anti-emetic activity)	Enhanced oral bioavailability of the drug with increased plasma drug concentration level.	Inhibition of CYP3A4 activity.	(Athukuri and Neerati, 2017)
13.	With glimepride (hypoglycemic drug)	Enhanced bioavailability and improved antidiabetic effect.	Inhibition of CYP2C9 activity.	(Veeresham *et al*., 2012)

Table 3: Interactions of Garlic with Prescribed Drugs

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

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

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

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 5: Interactions of Ginseng with Prescribed Drugs

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

Table 6: Interactions of Ephedra with Prescribed Drugs

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

Table 7: Interactions of Kava Kava with Prescribed Drugs

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

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