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Impact of Herbal Medicines on Conventional Drugs: An Overview

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Abstract: People misinterpret "natural" with "safe". Unaware of the fact that herbal medicine contains pharmacological active constituents in unknown quantities; people use herbal medicinal products (HMPs) carelessly. In the present scenario, people use conventional medicines with herbal medicines that are used as complementary. Impact of co-administration of complementary herbal products with conventional (prescription) drugs can results in severe interactions. Herb-drug interaction can occur through either pharmacokinetic or pharmacodynamic mechanisms. Herbs can alter the oral bioavailability of the co-administered conventional drug which can result in either synergistic or antagonistic effect on its action. So, the basic need of the present scenario is that physicians and consumers should know about the possible interactions and complications arising due to the concomitant use of conventional and complementary medicines as the use of herbal products have increased significantly. This review covers about the mechanism of herb-drug interaction with possible herbs that can interact with the possible drugs and the strategies that can help in the reduction of herb-drug interaction.

Keywords: Herb-Drug interaction, Herbal medicinal products, Conventional drugs, Cytochrome, Concomitant.

Introduction:

Before the advent of modern medicine, medicinal plants were used for the primary health care. Due to urbanization their use had declined but in the present scenario the use of herbs to treat diseases is increasing day by day (Ogbonnia *et al.* 2008). Various studies shows that more than 45% parents give herbal medications to their children for various medical conditions, 67% of women use herbs for perimenopausal symptoms and 45% use them in pregnancy (Ernst, 2004). Most people have misconception that herbal preparations being natural in origin are safe. In actuality, the fact is that these natural or herbal products contain a combination of potentially biological active compounds in unknown quantities and this increases the risk (Hussain, 2011). So, unaware of the fact people use herbal medicinal products (HMPs) with the conventional (western) medicines or prescription drugs as most of the herbal remedies are promoted as natural and safe (Homsy *et al.*, 2004). Actually it is not like this because some herbs are toxic (Ernst, 2004). According to WHO, about 70% of the world population takes (HMPs) as complementary or alternative medicine (Sheeja *et al*., 2006). It is reported that 40% of Americans consume herbal products. 60 - 85% of Africans, 14 – 16 % of Americans and 49.4% of Israeli use herbal products in combination with conventional medicine (Giveon *et al*., 2004; Kaufman *et al*., 2002; Tachjian *et al*., 2010; Van Wyk *et al*., 2009;). In addition to these facts less than 40% of patients disclose to their healthcare provider about the usage of herbal medicine coupled with the fact that even many physicians are unaware of the potential risks of herb–drug interactions (Klepser *et al.*, 2000). More than 70% of Indians use herbal drugs for their health (Vaidya and Devasagayam, 2007). Therefore, it is important to aware people about the possible herb-drug interactions (HDIs) as the concomitant use of herbal and western medicine has become a trend and this requires close attention. HDIs can occur either by pharmacokinetic or pharmacodynamic mechanisms (Hussain, 2011). HDIs may increase or decrease the pharmacological or toxicological effects of each other e.g. herb that is traditionally used to decrease glucose concentration in diabetes can cause hypoglycaemia if taken with conventional drugs due to synergistic effects (Agrawal and Raju, 2006). So this is the basic need of the present scenario that physicians and consumers should know about the possible interactions and complications arising due to the concomitant use of conventional and complementary medicines as the use of herbal products has increased significantly (Bodeker, 2007; Ernst, 2000; Mitra, 2007; Smith, 2000). Herbal medications have other challenges i.e. scientific misidentification, product contamination and adulteration, mislabeling, active ingredient instability, variability in collection procedures (Boullata and Nace, 2000). As these products have no standards and they are not regulated by FDA. Even like other pharmaceuticals they are not regulated for purity and potency (Hussain, 2011).

Definition and types of drug interactions:

When the effect of one drug gets altered by the presence of another drug, food or drink, it is called interaction. If any combinations of these cause undesired change in the condition of the patient then that interaction is of potential clinical significance. Drug interaction can be classified as: drug – disease, drug – herb, drug – drug and miscellaneous interactions (Hussain, 2011; Fig. 1). The drug – disease interaction is associated in patient suffering from any

disease e.g. renal or hepatic impairment, aplastic anemia, asthma, cardiac arrhythmia, diabetes, epilepsy hypothyroidism etc (Lambrecht *et al*., 2000). If the patient uses drug and herb concomitantly then, there are chances of drug–herb interaction as both contains pharmacological active compounds (Cupp, 1999). These interactions are discussed in detail later. Drug – drug interaction occurs between two drugs i.e. prescription drugs or over-the-counter drugs e.g. ciprofloxacin taken with antacids (Hussain, 2011). There are other examples of interaction of drug with dietary supplements, food, beverages, cigarette etc. For example, vitamin K and anticoagulants like warfarin, theophylline and tobacco (Jiang *et al*., 2004; Kruth *et al*., 2004). The mechanism of interaction can have pharmacokinetic or pharmacodynamic basis. The effect of interaction can be synergistic/additive or antagonistic/ negative (Hussain, 2011).

Composition of herbal products:

Among people, this is a big misconception that herbal products being natural in origin are safe but these products are composed of complex mixture of pharmacologically active phytochemicals which are present in unknown quantities, mostly of them are secondary metabolites generated through the shikimate, acetate–malonate, and acetate–mevalonate path-ways (Mok and Chou, 2006). These constituents include phenolics (such as tannins, lignins, quinolones, and salicylates), phenolic glycosides (such as flavonoids, cyanogens, and glucosinolates), terpenoids (such as sesquiterpenes, steroids, carotenoids, saponins, and iridoids), alkaloids, peptides, polysaccharides (such as gums and mucilages), resins and essential oils (Wang *et al.*, 2008). This complexity increases the risk of clinical drug interactions.

Mechanism of herb – drug interactions:

Herb–drug interactions can occur either by pharmacokinetic (PK) or pharmacodynamic (PD) mechanisms. Effect can be synergistic/additive or antagonistic/negative. Fig. 2 Pharmacodynamic interaction can be attributed to the ability of different chemicals to interact with common receptor sites and alter physiological environment while pharmacokinetic interactions attributed to altered absorption and distribution pattern as well as changes and competition in the metabolic and excretory pathways (Izzo, 2005). Pharmacodynamic interaction occurs through the interaction of herbal products with hepatic enzymes (Asdaq and Inamdar, 2010; Dasgupta et al., 2010; Kim *et al*., 2010a; Nivitabishekam et al., 2009; Van den Bout-van den Beukel *et al*., 2008). *In-vitro* and *in-vivo* studies indicated that the pharmacokinetic interactions involving altered drug concentration by co-administered herbs, may occur due to the induction or inhibition of hepatic and intestinal drug-metabolizing enzymes, particularly cytochrome P–450 (CYP) and/or drug transporters of efflux proteins such as P-glycoprotein (P-gp) (Boullata, 2005; Farkas *et al*., 2010; Meijerman *et al.*, 2006; Nowack, 2008). The modulation in the activity of CYP and drug transporters by herbal products may influence the oral bioavailability which alters the blood levels of affected drug (Brown *et. al*., 2008). Phytochemicals induce liver injury which includes elevation in transaminases, acute and chronic hepatitis, liver failure, veno-occlusive disorders, liver cirrhosis, fibrosis, cholestasis, zonal or diffusive hepatic necrosis and steatosis (Chitturi and Farrell, 2008; Chitturi and Farrell, 2000; DeLeve *et al*., 2002; Durazo *et al*., 2004; Lewis *et al*., 2006; Pierard *et al*., 2009; Saleem *et al*., 2010; Savvidou *et al*., 2007; Stedman, 2002; Wang *et al.*, 2009; Zhu *et al*., 2004). Bioactivation of CYP, oxidative stress, mitochondrial injury, and apoptosis can be the mechanism of liver injury (Cullen, 2005). Possible herb – drug interactions are listed in the table.

Modulation of metabolic enzymes:

Induction means the increase in intestinal and hepatic metabolic enzymes activity. So, concomitant use of enzyme inducing herbal product and the conventional drug causes increase in the rate of drug metabolism which affects oral bioavailability and the systemic disposition. This results in the sub-therapeutic plasma levels of the drug and ultimately, there is therapeutic failure. Some herbal products can cause inhibition of metabolic enzyme activities. This inhibition is usually competitive and dependent upon inhibitor concentration. These inhibitors are also substrates of enzymes (Zhang and Wong, 2005; Zhou, 2008). Due to the inhibition of metabolic enzymes results in drug accumulation causing toxicity. This is of particular concern with drugs having narrow therapeutic window or steep dose response.

CYP is the most important phase I drug-metabolizing enzyme system and it is responsible for the metabolism of many drugs. It is involved in oxidative, peroxidative and reductive biotransformation of xenobiotics and endogenous compounds (Hiratsuka, 2012; Nebert and Russell, 2002). CYP of families 1, 2 and 3 are principally involved in xenobiotic metabolism while other families play a major role in the formation and elimination of endogenous compounds such as hormones, bile acids and fatty acids. The most important CYP subfamilies responsible for drug metabolism in humans are 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4 and 3A5. Various families have substrate specificity (Amacher, 2010; Norlin and Wikvall, 2007; Ono et al., 1996; Wang and Chou, 2010). CYP3A4 is the most abundant of all isoforms. It is expressed in liver and intestine and it participates in the metabolism of about half of drugs in use today (Singh et al., 2011).

Herbal product e.g. St.John's wort (SJW, is an extract of the flowering portion of the plant *Hypericum perforatum* and contains biologically active compounds like hypericin and hyperforin) and various natural compounds isolated from herbs e.g. flavonoids, coumarins, furanocoumarins,

anthraquinones, caffeine and terpenes have been recognised as substrate inhibitors or inducers of various CYP enzymes depending on the species, tissue, dosage and duration of administration (Dietry Supplement-A; Hokkanen *et al*., 2011). The various drugs which are CYP and P-gp substrates includes tolbutamide, cyclosporine, tacrolimus, mycophenolic acid, carbamazepine, statins, digoxin, dihydropyridines (calcium channel blockers), phenprocoumon, warfarin, amitriptyline, tacrolimus, oxycodone, fexofenadine, irinotecan, theophylline, dextromethorphan, alprazolam, midazolam, methadone, loperamide, nevirapine, indinavir, and oral contraceptives whose pharmacokinetic profile is altered by SJW (Di *et al*., 2008; Greeson et al., 2001; Henderson et al., 2002; Hojo *et al*., 2011; Johne *et al*., 2002; Nieminen *et al*., 2010; Vlachojannis *et al*., 2011). St John's wort is one of the most widely used herbal antidepressants (Hoyland, 2011). Alteration in the blood serum concentration of cyclosporine due to SJW has led to organ rejection in patients (Ernst, 2002; Murakami *et al*., 2006). Interaction between SJW and oral contraceptives results in bleeding and unplanned pregnancies (Hu *et al*., 2005). SJW has most clinically significant pharmacokinetic drug interaction with the antidepressants as SJW itself is the popular herbal antidepressant. It acts through the inhibition of reuptake of neurotransmitters (dopamine, serotonin, noradrenaline). Its concomitant use with the conventional selective serotonin reuptake inhibitors (SSRI) like sertraline and paroxetine results in symptoms of central serotonergic syndrome (Barbenel *et al*., 2000; Birmes et al., 2003; Bonetto *et al*., 2007; Dannawi, 2002; Spinella and Eaton, 2002). Interaction between SJW and tolbutamide (hypoglycaemic drug) has increased the incidence of hypoglycemia (Mannel, 2004). A 21% decrease in the area under the plasma concentration–time curve of amitriptyline was observed due to concomitant use of SJW and amitriptyline for 2 weeks in 12 depressed patients due to induction of CYP 3A4-dependent metabolic activities as amitriptyline is a substrate of both CYP3A4 and P-gp (Johne et al., 2002). It is also reported that whole extract and major constituent especially hyperforin inhibit the metabolic activities of CYP 1A2, 2C9, 2C19, 2D6 and 3A4 (Hokkanen et al., 2011). Similarly, in garlic–saquinavir interaction, due to garlic-induced CYP3A4 induction there is 51% decrease in saquinavir oral bioavailability (Piscitelli et al., 2002). It also alters warfarin pharmacokinetics (Taki *et al*., 2012). *Ginkgo biloba* induces CYP2C19 which alters omeprazole metabolism (Yin *et al*., 2004). Grapefruit juice has inhibitory activity on CYP due to its flavonoid contents (Alvarez *et al*., 2010; Choi and Burm, 2006; Paine et al., 2008; Palombo, 2006; Quintieri *et al.*, 2008). One of the known CYP inhibitor is rotenone. It is a naturally occurring phytochemical present in many plants such as the jicama vine plant. By interfering with the electron transfer of the heme iron, it inhibits CYP activity (Sanderson et al., 2004). Other inhibitors are tryptophan (amino acid) and resveratrol (natural polymer) (Rannug et al., 2006). Echinacea that cause induction hepatic CYP3A4 and inhibition of intestinal CYP3A4. On the other hand, there are drugs that do not affect CYP3A4 and CYP2D6 activities in normal volunteers e.g. green tea, ginkgo, garlic, saw palmetto and Siberian ginseng (Hussain, 2011).

It is reported in a study that extracts of some hypoglycemic herbs like *Cymbopogon proximus, Zygophyllum coccineum* and *Lupinusalbus* reduced the activity of GST and GSH (Sheweita et al., 2002). Other study revealed that an herbal antioxidant having anti-inflammatory and antitumor properties, curcumin from *Curcuma longa* has increased the activity of GST and quinine reductase (Iqbal *et al.*, 2003). Another herb valerian which is used as an herbal sleeping aid has the potential of inhibition of UGT (Alkharfy and Frye, 2007). A traditional Japanese medicine, kampo which constitutes mixture of several medicinal herbs has inhibitory effect on some phase II enzymes. Components of kampo cause 50% inhibition of UGT2B7-mediated morphine 3-glucuronidation. Similarly, extracts of kanzo (*Glycyrrhizae radix*), daio (*Rhei rhizoma*) and keihi (*Cinnamomi cortex*) elicited more than 80% inhibition of morphine AZT glucuronidation (Nakagawa *et al*., 2009). Clinical significance of these study is yet to be determined but it can concluded that Phase II metabolic enzymes uridine diphosphoglucuronosyl transferase (UGT), *N*-acetyl transferase (NAT), glutathione *S*-transferase (GST) and sulfotransferase (ST), (these enzymes catalyze the attachment of polar and ionizable groups to phase I metabolites which helps in the elimination) can also play a role in HDIs.

Modulation of drug transporters:

The ATP-binding cassette (ABC) family of drug transporters plays significant roles in the absorption, distribution and elimination of drugs. P-gp, is the most important member of this family. It is expressed on the apical epithelial surfaces of the bile canaliculi of the liver, the proximal tubules of the kidneys, the pancreatic ductal cells, the columnar mucosal cells of the small intestine, colon and the adrenal glands (Degorter et al., 2012). P-gp helps in drug absorption and elimination from the intestines, liver, kidneys and brain. Specifically, it causes hepatobiliary, intestinal and urinary excretion of drugs and their metabolites (Szakács et al., 2008). So, the co-administered herbs can show affinity as substrates for its binding sites and presents a potential for alteration in the pharmacokinetic profile of the drug. Through a competitive and non-competitive mechanism, herbal drugs can inhibit or decrease the normal activity of drug transporters or they can cause induction of transporters by increasing the synthesis of mRNA of the relevant protein. Clinically important P-gp inhibitors includes phytochemicals such as flavonoids, furanocoumarins, reserpine, quinidine, yohimbine, vincristine, vinblastine (Eichhorn and Efferth, 2012; Iwanaga et al., 2010; Krishna and Mayer, 2001; Patanasethanont et al., 2007; Zhou et al.,

2004; Yu et al., 2011). Hyperforin, a major ingredient of St. John's wort, binds to orphan pregnane X receptor, resulting in a series of intracellular events leading to the expression of CYP 3A4 and P-glycoprotein (Hussain, 2011). Drug transporters play role in the mechanism of multiple resistance of cancerous cells to chemotherapeutic agents (Bosch, 2008; He et al., 2011). Interactions can be synergetic (or additive) in which the herbal drug potentiates the action of synthetic drugs (e.g. interaction between the anticoagulant warfarin with antiplatelet herb) or antagonistic (or negative), in which the herbal medicine reduces the efficacy of synthetic drugs (e.g. kava possesses dopaminergic antagonistic properties and hence reduce the pharmacological activity of the anti-Parkinson drug levodopa) (Izzo, 2005).

Modulation of biochemical parameters:

Another mechanism of interaction is the alteration of absorption of concomitantly administered drug. Such as, changes in the biological pH can alter the absortion of pH-dependent drugs i.e. ketoconazole and itraconazole. By formation of insoluble complexes through complexation and chelation. By competitively engage the sites of absorption can greatly affect the absorption of drugs. By decreasing gastrointestinal transit time such as anthranoid containing plants–cassia (*Cassia senna*), cascara (*Rhamnus purshiana*), rhubarb (*Rheum officinale*) and soluble fibers including guar gum and psyllium as they increase the motility of gastrointestinal tract with the risk of reduced absorption (Fugh-Berman, 2000). Other example is ginseng which produces inhibitory effects on gastric secretion (Suzuki et al., 1991). A herb *Polygonum paleaceum*, decreaes the motility of the gastrointestinal tract, inhibits defecation reflex and delays gastric emptying (Zhang, 2002).

Modulation in renal functions:

There are herbs that interact with the co-administered drug by altering the renal functions. They can alter the renal elimination as a result of inhibition of tubular secretion, tubular reabsorption or interference with glomerular filtration (Isnard et al., 2004). Some herbal products increase the glomerular filtration rate while some can act as direct tubular irritants (Al-Ali et al., 2003). For example, *Callilepis laureola* can cause damage to the proximal convoluted tubules and the loop of henle (Steenkamp and Stewart, 2005). Herbal products have one or more chemicals that interfere with the normal renal functions or they get converted to toxic metabolite that can also impair renal funtions. Herbs like *Aristolochia fangchi,* contains aristolochic acid that can form DNA adducts in renal tissues which leads to extensive loss of cortical tubules (Lai et al., 2010). Other herbs like *Pithecellobium lobatum* contains nephrotoxic djenkolic acid (Markell, 2010). Wild mushrooms especially, *Cortinarius* species contains nephrotoxic orellanine (Wolf-Hall, 2010). Liquorice root contains glycyrrhizic acid, rhubarb and star fruit contains high quantity of oxalic acid (Bihl and Meyers, 2001; Kataya et al., 2011; Wu et al., 2011). Some herbs have diuretic property that may increase the renal elimination of other drugs e.g. *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*) (Wojcikowski et al., 2009).

Activation of nuclear receptors:

Nuclear receptors (NRs) can also play role in drug interactions. Herbs can activate nuclear receptors that results in herb-drug interactions. These interactions are similar to drug-drug interactions but it is more complicated due to the presence of complexity of constituents (Sachar and Ma, 2013).

Risk reduction strategies:

It is clear now that conventional and herbal products are often used together which leads to clinically significant herb-drug interactions. So, there is a need to aware people about the truth of herbs that being natural is not the only criteria for the safe use of them. Herbs contain potentially active constituents that can interact with the co-administered drug resulting in the risk for the individual. Some of the methods to decrease the risk of herb-drug interactions are:

- Herbs should be included in the pharmacovigilance system to identify new herb associated risks. Its effectiveness depends on the involvement of prescriber, dispenser and user of herbal product to come forward with suspected and possible adverse effects (Barnes, 2003).
- Herbal products that are available in the market should have a package inserts with warnings regarding the herb-drug interactions. If possible these types of warnings should also be with the conventional drugs. Package inserts should also have the general advice of contact a physician or pharmacist in case of unexpected adverse effects (De Smet, 2006).
- Incorporation of herbal medicines into pharmacy records if information about a herbal product comes that it is not safe to sell this product without a pharmacist checking. This would bring the herbal products under a pharmacy-only medicine regimen (De Smet, 2006).
- Patient counseling should be done by the prescribers and dispensers of conventional drugs about the usage of any herbal product and also about the usage of any conventional medicines while prescribing or dispensing of herbal product. They should make aware

about the possibilities of herb-drug interactions (De Smet, 2006; Hussain, 2011). Some points on which attention should be paid:

1. Be aware about the patient history i.e. age, gender, chronically ill patients etc.

2. Drugs having narrow therapeutic index e.g. anticonvulsants, anticoagulants.

3. Drugs which are enzyme inducers or inhibitors.

4. Multiple drug combinations should be avoided.

5. Pharmacology of prescribed drug.

- Pharmacoepidemiological and experimental studies should be designed to understand more clearly about the herb-drug interactions (Lai et al., 2010).

Conclusion:

Presence of various biologically active constituents herbal medicines can potentially interact with the conventional drugs. Impact of herbal medicine administration on conventional drugs can result in either therapeutic toxicity or failure. This herb-drug interaction is based either on pharmacokinetic or pharmacodynamic mechanism. In the present article the possible herb-drug interactions are listed. Among them, some are clinically significant. More research is needed to understand properly about these herb-drug interaction. So, to avoid interaction between the herb and the conventional drug, the physicians and the consumers should have knowledge about the possible complications that can result due to concomitant use of them.

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