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Review Article

HOW A PHARMACIST CAN PREVENT HERB-DRUG INTERACTION: A REVIEW

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Abstract
The widespread use of the herbal drugs to an extent that it is used by three quarter of the world's population has given researchers an interesting topic to work on i.e., herb-drug interaction. Herb-drug interaction has been an area of major concern amongst the researchers as it is consumed by the major population along with the synthetic drugs without the concern of physicians. The herb-drug interaction can be in terms of pharmacological effects, toixicological effects and synergistic effects where in these effects either increase or decerease. Drug being substrates for metabolizing enzymes CYP-450 and p-gp are prone to these interactions. Herbal drugs are not under the supervision of regulatory bodies and sometimes they are treated as suppliments. This article highlights the mechanism of herb-drug interaction, nature and risks associated with herb-drug interaction and the role of pharmacists in prevention of herb-drug interactions.

Keyword: *Herb-drug interactions, pharmacokinetic, pharmacodynamic*

Introduction

The use of herbal medicines has gained huge importance throughtout the world for the treatment of various disorders. Since , people have the perception that herbal medicine are safe, it is sometimes prescribed with other synthetic drug without consultation of medical practioner. When herbal medicines and conventional synthetic drugs (prescription or non-prescription drugs) are taken together they can cause alterations in the way body or the drug acts, which can be sometimes harmless or fatal. Such alterations are termed as "Herb-drug interactions"[1]. The nature of herb-drug interaction is not always a chemical interaction, but sometimes the interaction involves a herb component which causes increase or decrease in the amount of drug in the blood stream [2]. World Health Organisation (WHO) has acknowledged the awareness for the herbal medicine and recently defined traditional medicine (including herbal drugs) comprised of therapeutic practises existing for several hundred of years even before there was any development of modern medicine. According to the estimation by WHO, three quater of the population worldwide uses herbs and other traditional medicines for treatment of diseases and it is also considered to be having a generous prospect in the gene therapy. Botanical products have increased in population for e.g., in the United States it has became a $1.5 billion industry a year. It is reported that 60% to 70% of the american population use botanical products, but most of them without the consultation of medical practioners. The interactions between the drugs the herbs and the food is still infancy. Some researchers reported that herb-drug interactions are less often seen and if there is any interaction,

conventional drugs usually affects as they are pharmacologically active [3-5].
Interaction between herbs and drugs increases or decreases the pharmacological or toxicological effects, whereas synergistic effect complicate dosing or long term medications. The herbal medicine are used widely says a US survey of adults regularly take prescribed medication, 18.4% of the population for the concurrent use of herbal products or high-dose vitamins, 61.5% of the population for using unconventional therapies do not disclose to their physicians [6].

Mechanism of herb drug interaction

Herb-drug interactions are mostly characterised by pharmacokinetic, pharmacodynaimic interactions. Factors like absorption, distribution, metabolism, protein binding or excretion of the drug affects the pharmacokinetic interactions. Some drugs are substrates for metabolizing enzymes CYP-450 and p-gp which have higher probability of interaction with herbal products. The metabolism phase is differentiated into two parts: Phase I reaction (biotransformation) which includes oxidation, hydroxylation, reduction, hydrolysis, a new functional group gets introduced into the substrate molecule an existing group gets modified for phase II transfer reactions, making xenobiotic more polar ready to excrete. Phase II reactions which are conjugating reactions involves enzymatic synthatese, whereas functional groups like alcohol, phenol,amine is masked by addition of a new group like acetyl sulphate, glucuronic acid whic increases the polarity of the drug or xenobiotic. Most of the drug undergoes phase I and II reactions [7-12].

Pharmacokinetic interactions

Absorption: Herbs which contains hydrocollodial carbohydrates such as gums, mucilages are poorly absorbable but soluble in water and they are bind to other drug especially when in whole or powdered form. For e.g., psyllium, rhubarb, flaxseed, marshmallow, aloe etc. [4]

Distribution

Highly protein bound drugs can be displaced by pain reducing salicylates contained in herbs. Foe e.g., black willow and meadowsweet can displace warfarinand carbamazepine which results in to adverse effects. Hence, these products should not be taken concurrently [4, 5].

Metabolism: Liquorice which is mostly used as aa herb not a sweetner reduces the metabolism of the corticosteroids hving an adverse or toxic effects from the evelopment of corticosteroids. As by recent reports of researchers St.John's wortcan induce hepatic microsomal enzyme in the CYP 450 system increasing the drug metabolism in the system, like digoxinand,theophyline, cyclosporine and protease inhibitor. These drugs are less effective so concurrent use of liquiorice along with these drugs are not recommended [4, 5].

Pharmacodynamic interactions

Pharmacokinetic interaction can result in additive, synergistic, antagonistic effects of supplementation combined with a drug. Boullata et al (2005) reported that medication possessing antiplatelet activity or with the potential to suppress the nervous system or to cause organ toxicity can increase further when used with dietary supplements. Many herbal drugs falls under this category where

pharmacodynamic interactions are difficult to predict or prevent [13].

Nature of herb drug interaction (HDI)

The complex nature of the natural product not only complicates the determination of herbal interactions it also complicates the manufacturing process; for eg drying process and extraction methods contributes to complexity. Herbal products are not regulated by the Food and Drug Administration and so there are no particular standards and can be easily substituted or adulteratedwith other natural products as different country have different regulations, in some country herbal products are mareted as dietary supplements. The united states FDA mandates that medicines have to be proven safe and herbal products do not fall into this category and they are not allowed to market for prevention of any diseases. In United Kingdom, Medical Control Agency(MCA) do not grant liscence to any product treated as food, no health claim or medical writing on the label. Labelling of herbal products may actually prevent misidentification of plants and not the adverse events reflects on the label. Since there were reports at first emerged a decade ago, a concern raised regarding our little knowledge about herbs and their potential for interaction with drugs that these incidents lead the herb-drug interaction looms largely over the world of medicine [24].

Risk of herb drug interaction

Concomitant use of herbs along with drugs plays an important role in herb-drug interaction that have a narrow therapeutic index. Examples include digoxin, antiepileptic drugs, immunosuppresants and warfarins. Patient population viz., elderly, critical care patients, patients with surgery, patients with liver or renal disease and patients receiving multiple medications [25].

St. John's Wort Drug Interactions

St. John's wort contains chemical constituents including phloroglucinols(hyperforin), naphthodianthones (hypericin and pseudohypericin), flavonoids, and xanthones, are widely used for the treatment of moderate depression and FDA also warned against the use of wort in combination with cyclosporine citing cases of acute rejection in heart transplants [29-31].

Current studies indicates hyperfoin as an active anti depressant constituent superimposing old study result and the abtidepressant mechanism includes inhibition of serotonin reuptake, increase in serotonergic and dopaminergic receptors, and increase affinity for GABAergic receptors [32, 33].

Research and invitro studies has shown the constituents of St. John's wort, especially hyperforin, are potent modulators of the nuclear xenobiotic pregnane X receptor, which regulates CYP3A and induces CYPA12, CYP2C9, CYP2C19, and CYP3A4. But it is also said that longer treatment (10days to 2 weeks) treatment should be carried on so that St.John wort doesnt induce CYP3A4 [34, 35].

A case report of a 80 year old man on long term digoxin therapy developed nodal bradycardia and bigeminy consuming St John's wort herbal tea (2,000 ml/day) which induces glycoproteins and there is a decrease in serum concentrations [36, 37]. The interaction of St. Johns wort with digixon varies on the preparation, mainly with the hyperfoin content and dose [38, 39].

Use of St. John's wort is given with selective serotonin reuptake inhibitors (SSRIs) buspirone, dextromethorphan, meperidine, monoamine oxidase inhibitors, SSRIs, tricyclic antidepressants, and triptans causes pharmacodynamic interaction because of overstimulation 5HT-1_A receptors in the central nervous system (CNS) with symptoms associated with mental status changes, tremor, autonomic instability, gastrointestinal complaints, headache, myalgias, and motor restlessness [40-42].

ROLE OF PHARMACIST IN PREVENTING HERB DRUG INTERACTION

Pharmacist plays an important role in preventing drug herb interaction by dispensing herbal medicine and taking patient care following medical history and medication profile to ensure the safety of the medicine. There are following questions to ensure the administration of medicine will be safe or not: wether the patient taking any other herbal products or other prescribed medicine for the same purpose as herbal product, is the patient allergic towards herbal products or any kind of allergic manifestations occur before due to use of any herbal products, for females wether they are pregnant or breast feeding. The doctor and pharmacist should know everything about the patients medication profile including any dietary supplements vitamins, minerals as well as medical history. The timing of the medication should be explained; for example it shold be instructed Take your medicine with a full glass of water. Avoid concurrent use of alcohol with medicine,consuming excessive quantities of chocolate, beverages containing caffeine coffee,tea,colas and If any questions or concerns about medicine or an adverse drug reaction or drug interaction is observed, consult your pharmacist or physician immediately.

Conflict of interest
None

Conclusion

The herbal dietary supplements have gained uttermost importance with the annual sales reaching $5 billion in 2007 in the United States. Though there is a dire need for more research regarding its potential interaction with prescribed medicines, preclinical, animal studies, premarketing and postmarketing surveillance inorder to ensure the safety of herbal medicines in the patients. Healthcare professionals, consumers, regulatory authorities should be aware of the herbal side effects and herb-drug interactions, which is discovered and reported and the physicians should explore herbal usage with their patients and provide caution. Patient should also be aware that FDA does not have any regulation for herbal medicine for safety and labelling of herbal products do not normally reflect their contents, adverse events attributed to different herbs due to misidientified herbs. For e.g., Siberian ginseng (*Eleutherococcus senticosus*) implicated in a case of neonatal androgenisation found on analysis to be an unrelated species, Chinese silk vine (*Periploca sepium*).

In HongKong, Chinese herbal preparation associated for the treatment encephalopathy and neuropathy made from the roots of long-dan-cao(*Gentiana rigescens)* due to another plant *Podophyllum emodi*. 2609 samples of Chinese medicines collected from eight hospitals in Taiwan, caffeine, paracetamol, indomethacin, hydrochlorothiazide and

prednisolone almost contain 23.7% pharmaceutical adulterants and Nonteroidal antinflammatory drugs, benzodiapenes mainly sold outside Asia. The compounds with Chinese patent include Miracle herb, Tung Shueh, Chuifong Toukwhan. At different times at 1974, the formulation was not good like aminopyrine, phenyl butazone, indomethacin, hydrochlorothiazide, chlordiazepoxide, diazepam, cortico-steroids, diclofenac, mefenamic acid, and dexamethasone.24 out of 250 Asian herbal products collected from California stores, USA, contained lead(at laest 1ppm), products also contain arsenic, mercury.

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Table 1: Comparision of study methods available for HDI

Methods	Advantages	Limitations	
In vitro studies	Easy to perform, good for high throughput screenings, results are closer to human.	Poor reproducibility of results, poor correlation to clinical situation.	[14,15]
In vivo studies	Concentration and bioavailability of active components are taken into consideration. Differences in biology and pharmacokinetics of species.	Results are difficult to interpret, variation in species, use of variable dosage forms.	[14,15]
Case reports	Providing information on HDI.	Poor statistical values.	[10]
Human studies	Extrapolative data on interactions	Expensive, genetic variation in enzyme activity.	[16,14]

Table 2: Methods for inhibition of CYP

Methods	Mechanism	Advantages	Disadvantages	
Fluorescence (high throughput)	Pro-fluorescent substrate metabolized to fluorescent product.	Fast, sensitive, cost effective, measures enzyme activity.	Recombinant enzymes needed as probes.	[17-19]

Luminescence (high throughput)	Pro-luminescent substrate metabolized to luminescent product.	Very sensitive	Work-up reagent required. Recombinant enzymes needed.	[20, 21]
Radiometric (low throughput)	Release of radiolabel on metabolism of substrate	Fast and accurate.	Large amount of radiolabelled substance used.	[17, 18]
LC_MS/MS (Medium throughput) CYP450-CO complex assay	Standard method for all interaction assessment. CYP450 microsomes quantitated using characteristic absorbance peak at 450nm	Sensitive and specific. Simple, less laborious, reliable, reproducible	Expensive Less sensitive	[22, 23]

Table 3: Documented Herbal-Drug Interactions [26-28]

Herbal	Drug	Comment	Mechanism
Betel nut (*Areca catechu*)	Procyclidine	Betel nut has cholinergic activity	↓ drug effect
Boldo (*Peumusboldus*) (in combination with fenugreek)	Warfarin	Boldo constituents have antiplatelet activity	↑ bleeding risk
Capsicum (*Capsicum annuum*)	ACE inhibitor	Increased risk of cough	↑ drug toxicity
Danshen (*Salvia miltorrhiza*)	Warfarin	Danshen decreases half-life of warfarin	↑ drug effect
Dong quai (*Angelica sinensis*)	Warfarin	Dong quai contains coumarin derivatives; danshen decreases half-life of warfarin	↑ drug effect
Fenugreek (*Trigonella*species) in combination with boldo	Warfarin	Fenugreek constituents have antiplatelet activity	↑ bleeding risk
Fiddleheads	Warfarin	Fiddleheads containsvitaminK	↓ drug effect

Garlic (*Allium sativum*)	Warfarin	Garlic has antiplatelet activity	↑ drug effect
Garlic (*Allium sativum*)	Saquinavir	Induction of CYP3A4 enzymes	↓ drug effect
Ginger (*Zingiberofficinale*)	Phenprocoumon	Ginger can inhibit thromboxane synthetase and/or decreases platelet aggregation	↑ bleeding risk
Ginkgo (*Ginkgo biloba*)	Aspirin	Ginkgo has antiplatelet activity	↑ bleeding risk
Ginkgo (*Ginkgo biloba*)	Haloperidol	Ginkgo may scavenge free radicals produced by hyperdopaminergic activity	↓ drug toxicity
Ginkgo (*Ginkgo biloba*)	Ibuprofen	Ginkgo has antiplatelet activity	↑ bleeding risk
Ginkgo (*Ginkgo biloba*)	Omeprazole	Induction of CYP2C19 enzymes	↓ drug effect
Ginkgo (*Ginkgo biloba*)	Trazodone	Ginkgo may have GABA-ergic activity	↑ drug effect
Ginkgo (*Ginkgo biloba*)	Valproic acid	Contaminants of leaf/seed that may contain neurotoxins	↑ drug toxicity
Ginseng, American (*Panaxquinquefolius*)	Warfarin	Unknown	↓ drug effect
Ginseng, Asia (*Panax ginseng*)	Phenelzine	Unknown	↑ drug toxicity
Ginseng, Siberian (*Eleutherococcussenticosus*)	Digoxin	False elevation of digoxin by unknown mechanism	No effect
Green tea (*Camellia sinensis*)	Warfarin	Green tea contains vitamin K	↓ drug effect
Kava (*Piper methysticum*)	Alprazolam	Additive CNS depressant effect	↑ drug effect

Kava (*Piper methysticum*)	Levodopa	Kava may antagonize dopamine	↓ drug effect
Lycium (*Lyciumbarbarum*)	Warfarin	Induction of CYP2C9 by Lycium	↑ bleeding risk