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Herb-drug interaction: A review

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ABSTRACT

Plants have been providing vital source of medicines since ages. Earlier these are used by communities in folk medicine and later accepted by conventional western medicine as their efficacy was established. Any pharmacological alteration caused by herbal substances to another prescription medication (diagnostic, therapeutic or other action of a drug) in or on the body is herb-drug interaction. For the treatment of major ailments herbs are often administered concomitantly with therapeutic drugs, raising the potential for herb–drug interactions. Herb might alter the effects of co-administered drugs and the consequences can be beneficial, undesirable or harmful effects. Herbal medicines are mixtures of more than one active ingredient. The multitude of pharmacologically active compounds obviously increases the likelihood of interactions. As synthetic drug usually contains single chemical entity, the chance of herb–drug interactions is theoretically higher than drug–drug interactions. Interactions between herbs and drugs may alter the pharmacological or toxicological effects of either components. Synergistic effects may disturb the dosing of long-term medications. Herbal medicines are abundant: the lack of reports of adverse events and interactions possibly reflects a combination of underreporting and the benign nature of most herbs used. This article provides brief idea about practitioner can change the current situation and apply their knowledge in providing health information about herb-drug interaction.

Key words: Drug, herbal medicine, interaction, pharmacological effect

INTRODUCTION

Consumption of herbal and dietary supplements is extremely common: in one of the survey of adults at United States who frequently take prescription medication, 18.4% reported the simultaneous use of at least one herbal product or high-dose vitamin and 61.5% of those who used alternative therapies did not tell such uses to their physicians. In UK, the prevalence of use of herbal medicinal products (HMPs) is high and continues to increase (Hunt and Ernst, 2010) as well as in other parts of the world (Merritt-Charles, 2011). The safety issues associated with the administration of HMPs should be known (Ernst, 2000; Ernst et al., 2006; Paul, 2011). Some of pharmacologically active ingredients which are present in HMPs might interact with synthetic drugs (Ernst, 2000) which, in turn, could endanger the health of patients (Izzo and Ernst, 2009). During the last century's industrialization and urbanization declined thier use in western developed countries. However, a new resurgence in medicinal plants consumption was observed in the past two decades. About 70% of the world population according to the WHO currently uses medicinal herbs as complementary or alternative medicine. It is estimated that over 40% of the adult American population consume herbal products for one or the other medical reasons. A common problem is that the phrase "herb-drug interaction" usually appears in the media, without much explanation and understanding of the pharmacodynamics of the same. Herbal medicines are abundant: the lack of reports of adverse effects and interactions possibly reflect a combination of underreporting and the benign nature of maximum

herbs used. Experimental data in the field of herb drug interactions are inadequate resultant to infrequent case reports. The factual incidence of drug interactions is substantial but unknown. Polypharmacy is very common in clinical practice and to the mixture physicians prescribe; patients add several over-the-counter medications, minerals, vitamins, herbs, and foods. All consumed ingredients have the chance to interact. Some herbs are dangerous to patients who are already taking prescription medications. The problems get increased for those patients currently taking various medications, frequently recommended by different physicians who may or may not be in contact with each other concerning their medical reasoning.

MECHANISM OF HERB-DRUG INTERACTIONS

There are mainly two types of interactions occur between herbs and drugs that can be either pharmacokinetic or pharmacodynamics (Izzo et al., 2002). The factors affecting herb drug interactions have been presented in Fig.1.

Pharmacokinetic interactions

Any herbal preparation alters the absorption, distribution, metabolism, protein binding and excretion of prescribed medication that results in changed levels of the medicine or its metabolites that is called pharmacokinetic interactions. Most of the recent evidence of pharmacokinetic drug interactions contains metabolizing enzymes and drug transporters. Most herbal drug interactions are associated with oxidative metabolism by the cytochrome P-450 system (CYP) such as glutathione S-transferases and uridine di-phosphoglucuronyl transferases (UGTs) or by the influence of an herbal product on the efflux drug transporter P-glycoprotein. (Zhou et al., 2003; Zhou et al., 2004).

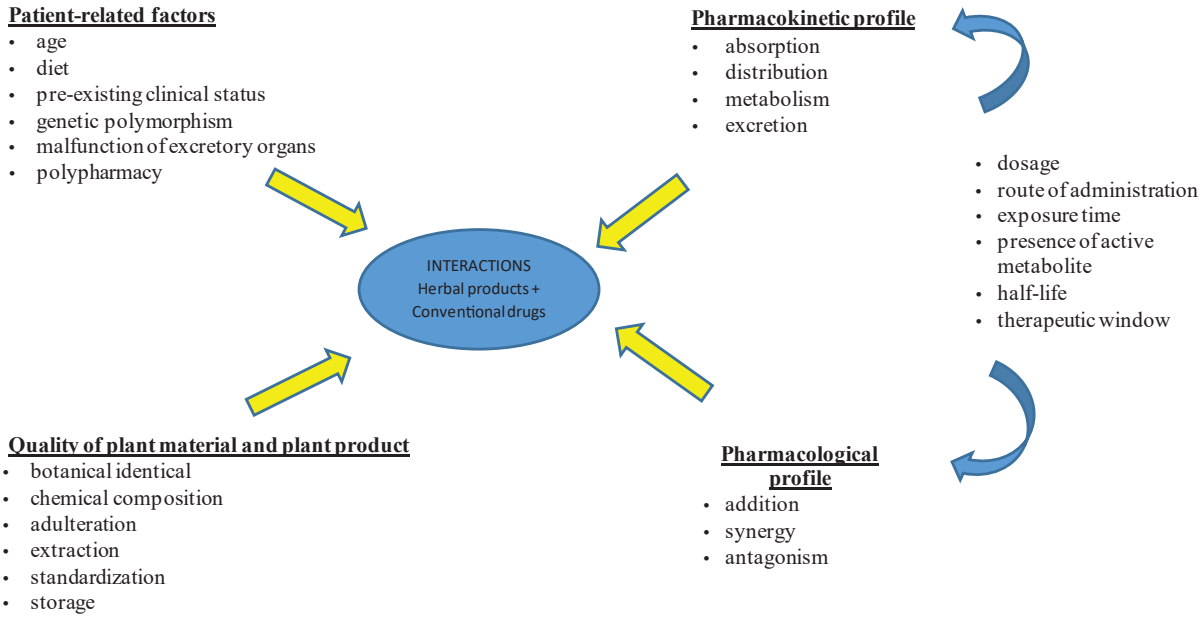

Fig. 1 Factors affecting herb drug interaction

Absorption

Herbs affecting intestinal motility and changes in intestinal pH will alter absorption of other drugs. Also, oral bio-availability of medications can be reduced when they are combined with soluble and insoluble fibers; for example: Aloe leaf, Guargum and Senna, are common uses in herbal weight-loss products, exert a laxative effect that may reduce intestinal transit time and alter drug absorption, *St. John's Wort* boosts intestinal P-glycoprotein and reduce the absorption of common P-glycoprotein substrates, such as dioxin. Such effects may be preventing if the drug is consumed 1 hour before

or 2 hours after the herb. (Roby et al., 2000; Wang et al., 2001**).** Some clinical trial demonstrates that patients taking lovastatin with pectin or oat bran have shown increased low-density-lipoprotein (LDL) levels, which reverted to normal after fiber supplementation was stopped. The possible reason of this interaction was reduction in lovastatin absorption due to binding of lovastatin by pectins or bran fibers in the intestinal lumen.

Distribution

A drug with high plasma protein binding like warfarin, carbamazepine, that has a lesser volume of distribution can be displaced by a herb competing for the similar binding sites. Drug displacement cause rise in serum drug levels and lead to an increase in therapeutic effect.

Metabolism

The main site of drug metabolism are liver, intestines, kidneys, and lungs, of those, the liver is the major site of drug metabolism. Drug metabolic pathways have been classified into 2 groups-phase I and phase II. Phase I enzymes such as cytochrome P450 oxidases are a super family of hemoproteins, introduce reactive or polar groups into xenobiotics. They oxidize mainly non-polar molecules by increasing their polarity and allowing them to be excreted in the urine. The major CYP isoforms are 1A2, 2D6, 2C9, 2C19, and 3A4 (Zhou et al., 2003; He et al., 2010). An assessed 60% of drugs are metabolized and excreted through the CYP3A4-dependant pathway. Phase II enzymes follow a different chemical process referred to as conjugation. Phase I and phase II activities must be synchronized or the induction of phase I could cause generation of too many transitional metabolites for phase II to process. Likewise, excessive phase II substrates can lead to surge in reactant concentrations, sometimes with fatal consequences. For example, acetaminophen (N-acetyl-p-amino-phenol) which is mainly metabolized by CYP2E1, also CYP1A2, 2A6, 2D6, and 3A4 playing minor role. When acetaminophen undergo through phase I enzymes, it metabolizes into N-acetyl-p-benzoquinone-imine (NAPQI), a toxic intermediate that phase II enzymes must then diminish and conjugate with glutathione before the final substrate is excreted in the urine. Too much phase I activity can overcome phase II enzymes, resulting in a build-up of NAPQI that leads to hepatic centrilobular necrosis. St. John's Wort (Hyperforin) induces the cytochrome P450 enzymes which are responsible for the metabolism of several drugs (Moore et al., 2000). Other examples, St. John's Wort reduce the efficacy of the oral contraceptive pill or blood levels of warfarin, digoxin, protease inhibitors, theophylline and carbamazepine. Likewise, prodrugs can be activated by phase I oxidation and create toxicity. Thus, induction of phase I by herbs could supposedly result in a toxic increase in serum drug concentrations, while this has not been clinically accepted.

Some herbs decrease the production of the enzyme essential for break down the drug, hence increasing the drug levels. It will take several days or weeks to develop fully, enzyme inhibition can occur within 2-3 days resulting in a quick development of toxicity for example, *Licorice* decreases the metabolism of corticosteroids, leading to adverse and toxic effects from the build-up of corticosteroids. *Echinacea* and *Chamomile* decrease the cytochrome P450, isoenzyme CYP3A4. Simultaneously use with drugs like alprazolam, simvastatin, calcium-channel blockers, and protease inhibitors could possibly rise serum drug levels and adverse effects. Some studies revealed that grape fruit irreversibly inhibit CYP3A4 activity *in vitro*, and taking as little as 200 ml can result in clinically significant increases in serum drug concentration. Variation in CYP and Pgp activities are vital factors of drug bioavailability, therapeutic potential, and the risk of adverse events.

Excretion

Changes in excretion of drug and their metabolites also affect serum drug levels of other drug for example, Licorice (Glycrrhiza) consumption can lead to extra mineralocorticoid activity that is exhibited by inhibited renin levels, herbal diuretics like Ham's worth, Horse tail, Hibiscus, etc., are quite weak and unlikely to cause large problems.

Pharmacodynamic interactions

Pharmacodynamical interactions are related to the pharmacologic activity of the interrelating agents and can disturb organ systems, receptor sites, or enzymes. An example of additive interaction is when an herbal with hypnotic activity like Valerians is ingested with benzodiazepines and anticoagulant action of some drugs like warfarin is enhanced by gingko, garlic and ginger. Other example like, St John's Wort (Hypercin) together with other serotonergic drugs shows the additive effect of the serotonin syndrome which is characterized by altered mental status, autonomic dysfunction and neuromuscular abnormalities. And Kava that slow down the central nervous system (CNS) is administered with CNS depressant drugs shows the additive interaction. Herb--drug pharmacodynamic interactions would, therefore, involve changes in the pharmacological effects of the drug through additive, synergistic or antagonistic actions (Gardiner, 2008). Some of the important documented herbs causing interaction with drugs have been presented in Table. 1.

Table 1. Effects of some herbs drugs interaction

Sl.	Herb	Use	Interact with	Effect
1	*Aloe vera*	Strong cathartic	Thiazide diuretics, Cardiac glycosides	Can cause electrolyte imbalance and hypokalemia
2	Bearberry (*Arctostaphylos uva-ursi*)	Urinary tract, antibacterial, astringent, diuretic	Cranberry juice, Urinary acidifiers	Active compound released in alkaline urine, inactivated by urinary acidifiers
3	Clove (*Syzygium aromaticum*)	Toothache,	Anticoagulants, Anti-epileptic	May diminish blood clotting and antiepileptic activity
4	Garlic *(Allium sativum)*	Hyperlipidemia	Antiplatelet agents, Anticoagulants	Inhibits platelet aggregation; Additive anticoagulant, antiplatelet effects
5	Ginger (*Zingiber officinale*)	Motion sickness, nausea, arthritis	Antiplatelet agents, Anticoagulants	May have additive anticoagulant, antiplatelet effects Inhibits thromboxane synthetase
6	Milk thistle (*Silybum marianum*)	Hepatitis, Cirrhosis, Diabetes, Heartburn, Dyspepsia	Antiarrhythmic drugs	Potentiates drug effect
7	Senna (*Senna acutifolia, S.augustifolia, Senna alexadrina)*	Constipation	Digitalis, Diuretics	Potentiate drug toxicity and chronic use may cause hypokalemia
8	St. John's Wort (*Hypericum perforatum)*	Depression	Antidepressants, Sympathomimetic amines, Ma Huang, pseudoephedrine, yohimbine	Herb may selective serotonin reuptake inhibitor effects or have monoamine oxidase inhibitor; Possible hypertensive crisis
9	Turmeric (*Curcuma longa)*	Dyspepsia	Antiplatelet agents	Herb contains curcumin; may potentiate antiplatelet activity
10	Cascara (*Rhamnus purshiana*)	Stimulant laxative	Cardiac glycosides, Thiazide diuretics	May potentiate drug toxicity, can cause electrolyte imbalance and hypokalemia

Antagonistic interactions

An example of antagonistic interaction is when an herb like Ephedra or caffeine-containing herbs (cola nut, guarana, mate) used as a stimulant, appetite suppressant, concentration aid, decongestant, and to treat hypotension associated with anesthesia is ingested with antihypertensive medications which antagonize the effects antihypertensive medications. In addition, herbals with the possibility to cause organ toxicity may cause further risk of toxicity when drugs with similar toxicity are administered simultaneously such as when the hepatotoxic herbal comfrey is ingested with large and sustained doses of acetaminophen.

CONCLUSION

Cataloging of herbal products may not accurately reveals their components and adverse effects or interactions attributed to certain herbs may actually be due to misidentified plants, pharmaceutical drugs, or heavy metals. The statement that herbal medicines also have adverse effects and can cause potential drug-herb interactions, it does not suggest that their use should be diminished. Most herbal drugs may provide the chance for enzyme induction/inhibition to take place and have better safety profiles. The ultimate issue is that herbal drugs should be considered as medicines, their interactions and adverse effects considered.

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