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HERB-DRUG INTERACTION: AN OVERVIEW

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ABSTRACT: Plants have always provided an important source of medicines. They may be used by natives in folk medicine and later adopted by conventional western medicine as their efficacy was confirmed. Any pharmacological modification caused by herbal substances to another prescription medication (diagnostic, therapeutic or other action of a drug) in or on the body. An herb might increases or decreases the effects of co-administered drugs. Consequences can be beneficial, undesirable or harmful effects. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications eg: Herbs traditionally used to decrease glucose concentrations in diabetes-I could theoretically precipitate hypoglycemia if taken in combination with conventional drugs. Herbal medicines are ubiquitous: the dearth of reports of adverse events and interactions probably reflects a combination of underreporting and the benign nature of most herbs used. This article provides brief idea about pharmacist can change the present scenario and utilize their knowledge in providing health information about herb-drug interaction.

INTRODUCTION: Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications. Use of herbal and dietary supplements is extremely common: in one US survey of adults who regularly take prescription medication, 18·4% reported the concurrent use of at least one herbal product or high-dose vitamin (and 61·5% of those who used unconventional therapies did not disclose such use to their physicians) [1].

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A basic problem is that the phrase "herb-drug interaction" routinely appears in the media, without definition and an assumption that everyone knows what is meant. Herbal medicines are ubiquitous: the dearth of reports of adverse events and interactions probably reflects a combination of underreporting and the benign nature of most herbs used. Experimental data in the field of herb drug interactions are limited, case reports scarce, and case series rare.

This lack of data is also true of drug drug interactions: published clinical studies are mainly case reports (controlled trials are scarce, since the random assignment of patients to trials that examine unintended effects is not ethical). The true prevalence of drug interactions is substantial but unknown. One study of 1000 elderly people admitted to a hospital from the emergency department found that 538 patients were exposed to

1087 drug-drug interactions; 30 patients experienced adverse effects as a consequence of these interactions [2].

In clinical practice, polypharmacy is common, and to the mixture physicians prescribe, patients add various over-the-counter medications, vitamins, herbs, and foods. All ingested substances have the potential to interact. Herbs are coming under increasing attack for being potentially dangerous to patients who are already taking prescription medications. The concerns are multiplied for those patients currently taking multiple medications, often prescribed by multiple physicians who may or may not be in communication with each other regarding their medical reasoning.

Mechanism of herbal-drug interactions: When there are any interactions between herbals and drugs occur that can be caused by either pharmaco-kinetic or pharmacodynamic mechanisms.

Pharmacokinetic interactions: When an herbal changes the absorption, distribution, metabolism, protein binding, or excretion of a drug that results in altered levels of the drug or its metabolites that is called pharmacokinetic interactions. Most of the current evidence of pharmacokinetic drug interactions involves metabolizing enzymes and drug transporters [1].

Although drug interactions can involve enzymes such as glutathione S-transferases and uridine diphosphoglucuronyl transfereases (UGTs), most herbal drug interactions are related to oxidative metabolism by the cytochrome P-450 system (CYP) or by the effect of an herbal on the efflux drug transporter P-glycoprotein.

Interference with Absorption: Oral bioavailability of medications can be decreased by this latter mechanism when they are combined with soluble and insoluble fibers; for example, with psyllium (*Plantago psyllium*) or tannins like those found in tea (*Camellia sinensis*), pomegranate (*Punica granatum*), cinnamon (*Cinnamomum* spp), and rhubarb (*Rheum* spp) [3]. This was demonstrated in a clinical trial in which patients taking lovastatin with pectin or oat bran experienced an increase in low-density-lipoprotein (LDL) levels, which returned to normal after fiber supplementation was discontinued [4].

The most likely cause of this interaction was a decrease in lovastatin absorption due to binding of lovastatin by pectins or bran fibers in the intestinal lumen [5].

Drug Metabolism: The liver, intestines, kidneys, and lungs are the sites of drug metabolism and pharmacokinetic interactions [6-9]. Of those, the liver is the major site of drug metabolism, with the intestines playing a secondary yet potentially important role [10]. Drug metabolic pathways historically have been classified into 2 groups-phase I and phase II. These 2 phases work in sequence, with most metabolites of phase I passing through phase II. Phase I enzymes are a super family of hemoproteins called cytochrome P450s (CYP). They oxidize relatively non-polar molecules, increasing their polarity and allowing them to be excreted in the urine. The main CYP isoforms are 1A2, 2D6, 2C9, 2C19, and 3A4 [2, 8, 9].

An estimated 60% of drugs are metabolized and excreted via the CYP3A4-dependant pathway [11]. Phase II enzymes follow a different chemical process, which is referred to as conjugation. Phase I and phase II activities must be coordinated or the induction of phase I could cause production of too many intermediate metabolites for phase II to process. Similarly, excessive phase II substrates can lead to an increase in reactant concentrations, sometimes with fatal results. For example, CYP2E1 is the major isoform responsible for the bioactivation of acetaminophen (N-acetyl-pamino-phenol), with CYP1A2, 2A6, 2D6, and 3A4 playing minor roles in this process [12].

When acetaminophen passes through these phase I enzymes, it metabolizes Nacetyl- p-benzoquinone-imine (NAPQI), a toxic intermediate that phase II enzymes must then reduce and conjugate with glutathione before the final substrate is excreted in the urine. Excessive phase I activity can overwhelm phase II enzymes, resulting in a build-up of NAPQI that leads to hepatic centrilobular necrosis [13].

Similarly, prodrugs, which become active only after being modified in the body, can be activated by phase I oxidation and create toxicity. Thus, induction of phase I by herbs could theoretically result in a toxic increase in serum drug concentrations, although this has not been clinically documented [13].

Grapefruit (*Citrus paradisi*) has been shown to irreversibly inhibit CYP3A4 activity in vitro, and consuming as little as 200 ml (6.67 oz) can result in clinically significant increases in serum drug concentration [14, 15, 16]. Modulation of CYP and Pgp activities are important determinants of drug bioavailability, therapeutic potential, and the risk of adverse events.

Altered Metabolism: Bioactive compounds in herbs are well-known modulators of CYP and Pgp expression and activity *in vitro* and *in vivo* [2, 11]. A compound isolated from *Berberis* (*Mahonia*) spp, 5'-methoxyhydnocarpin (5'-MHC), inhibits bacterial efflux pumps in vitro and may have clinical relevance for antibiotic-resistant strains of bacteria. It may also have promise in cancer chemotherapy, as cancer cell Pgp can also be inhibited by 5'-MHC.

Recent research also has identified clinically relevant CYP genetic polymorphisms [17]. There are an estimated 55 human CYP isoforms, and sexual dimorphisms have recently been detected for CYP1A2 and 3A4 isozymes. SJW induced CYP1A2 in females but not males in 2 clinical trials. Allelic variations alter CYP isozyme kinetics and explain changes in rates of drug metabolism [18]. Serum theophylline concentration, which is primarily metabolized by CYP1A2, was not affected by 300 mg SJW (TruNature®, Leiner Health Products, Carson, Calif, standardized to 0.3% hypericin) 3 times daily in males [19].

In another study, 300 mg SJW (Wild Oats Markets, Inc, Boulder, Colo, standardized to 0.3% hypericin) 3 times daily induced CYP3A4 activity to a significantly greater extent in women than in men [20]. A time-dependent effect of drugs and herbs on CYP also exists with potentially important clinical consequences. Acute administration can decrease drug clearance, whereas long-term administration can induce drug metabolism, either by increasing protein synthesis (CYP3A) or via enzyme stabilization (CYP2E1) [11].

Acute administration of the SJW extract hyperforin initially inhibited human hepatocyte CYP3A4 activity *in vitro*, and then induced the enzyme with continued dosing [21]. Due to difficulties in identifying the active constituents responsible for the modulation of CYP enzymes, the lack of standardization in the dietary supplements industry, and the influence of genetic polymorphisms on drug clearance, predicting herb-drug metabolic interactions in patients are difficult. To gain a working understanding of herb-drug interactions, clinicians must be able to accurately interpret studies and apply them to their patients' specific circumstances.

Pharmacodynamic Interactions: Pharmaco-dynamic interactions are related to the pharmacologic activity of the interacting agents and can affect organ systems, receptor sites, or enzymes. A Pharmacodynamic interaction may occur when herbals that possess antiplatelet activity are administered with antiplatelet/anticoagulant drugs, thus increasing the risk for bleeding. Other examples are when herbals that depress the central nervous system (CNS), such as kava, are administered with CNS depressant drugs or when herbals that may lower blood glucose are given with antidiabetic drugs.

An example of an antagonistic interaction is when an herbal with high caffeine content, such as guarana, is administered with a sedative-hypnotic. In addition, herbals with the potential to cause organ toxicity may cause further risk of toxicity when drugs with similar toxicity are administered concurrently, such as when the hepatotoxic herbal comfrey is given with large and prolonged doses of acetaminophen.

SOME SELECTED HERB-DRUG INTERACTION

S. No.	HERB	COMMON USE	MAY INTERACT WITH	POTENTIAL EFFECT
1	*Aloe vera*	Strong cathartic	Cardiac glycosides, Thiazide diuretics [23]	Can cause electrolyte imbalance and hypokalemia; May potentiate drug toxicity
2	Bearberry	Urinary tract antibacterial, astringent, diuretic	Urinary acidifiers, Cranberry juice [22]	Inactivated by urinary acidifiers; active compound released only in alkaline urine.
3	Cascara	Stimulant laxative	Cardiac glycosides, Thiazide diuretics [23]	Can cause electrolyte imbalance and hypokalemia; May potentiate drug toxicity

4	Garlic *(Allium sativum)*	Hyperlipidemia	Anticoagulants Antiplatelet agents [22, 24]	Inhibits platelet aggregation; Additive anticoagulant, antiplatelet effects
5	Ginger	Motion sickness, nausea, arthritis	Anticoagulants, Antiplatelet agents [22,24]	Inhibits thromboxane synthetase; may have additive anticoagulant, antiplatelet effects
6	Karela (Bitter melon)	Diabetes mellitus	Hypoglycemic drugs[24]	Potentiates drug effect
7	Ma-huang Ephedra, squaw tea, mormon tea, popotillo, sea grape *(Ephedra* species*)*	Asthma, weight loss	Oxytocin, Methyldopa, b-blockers, Caffeine, Monoamine oxidase inhibitors, Theophylline, Sympatho-mimetics, St. John's wort, Guanethidine, Cardiac glycosides [23, 25]	Increased sympathomimetic action; may induce hypertension, CNS stimulation
8	Senna *Cassia acutifolia, C.augustifolia, Senna alexadrina)*	Constipation	Digitalis, Diuretics [23, 10]	Chronic use may cause hypokalemia and potentiate drug toxicity
9	St. John's Wort (*Hypericum perforatum)*	Depression	Antidepressants, sympathomimetic amines, Ma Huang, pseudoephedrine, yohimbine [23,24]	Herb may have monoamine oxidase inhibitor or selective serotonin reuptake inhibitor effects; Possible hypertensive crisis, serotonin syndromes
10	Turmeric Tumeric, indian saffron *(Curcuma longa)*	Dyspepsia	Antiplatelet agents [22]	Herb contains curcumin; may potentiate antiplatelet activity

Clinical decision making: Pharmacist can play a vital role in preventing drug herb interaction to occur by appropriately dispensing medicine and taking due care of patient's history and medication profile. Future research will continue to elaborate the complex interactions of drugs and herbs, but clinicians need to be able to provide educated, well thought-out information to patients now. If well-designed clinical trials exist for a given herb-drug interaction, then the answer is easy because data would support or discourage a specific combination of herbs and drugs.

If enough *in vivo* data exist for a strong interaction (either induction or inhibition) between an herb and CYP or Pgp, then similar herb-drug interactions could be expected from other drugs metabolized by the same CYP and Pgp enzymes. in vitro data and case reports may or may not be accurate and should be evaluated individually for their merit. Most clinicians do not have time to review the minutiae of these studies.

In the absence of clinical trials of herb effects on drug clearance, the narrower the therapeutic window of a drug, the stronger the warnings against combining herbs and drugs. Regardless, it would be prudent to monitor appropriate laboratory values if there is any reason for concern. Taking a conservative approach when advising patients about combining herbs and drugs will help protect them against adverse interactions.

CONCLUSSION: Labelling of herbal products may not accurately reflect their contents, and adverse events or interactions attributed to specific herbs may actually be due to misidentified plants, pharmaceutical drugs, or heavy metals. For example, a "Siberian ginseng" (*Eleutherococcus senticosus*) product implicated in a case of neonatal androgenisation was found on analysis to be an unrelated species, Chinese silk vine (*Periploca sepium*).

In Hong Kong, encephalopathy and neuropathy associated with a Chinese herbal preparation purportedly made from the roots of long-dan-cao (*Gentiana rigescens*) turned out to be due to another plant *Podophyllum emodi*. The addition of pharmaceutical drugs to "herbal" products is a particular problem with Chinese patent medicines. Of 2609 samples of traditional Chinese medicines collected from eight hospitals in Taiwan, 23.7% contained pharmaceutical adulterants, most

commonly caffeine, paracetamol, indomethacin, hydrochlorothiazide, and prednisolone. Non-steroidal anti-inflammatory drugs and benzodiazepines have been found in many Chinese patent medicines sold outside Asia; these compounds include Miracle Herb, Tung Shueh, and Chuifong Toukuwan. The latter preparation is notorious: at different times since 1974, the formulation has contained aminopyrine, phenyl butazone, indomethacin, hydrochlorothiazide, chlordiazepoxide, diazepam, cortico-steroids, diclofenac, mefenamic acid, and dexamethasone.

Heavy-metal contamination is not uncommon in Asian herbal products. 24 of 251 Asian patent medicines collected from herbal stores in California, USA, contained lead (at least 1 ppm); 36 products contained arsenic, and 35 contained mercury.

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