



HERB-DRUG INTERACTIONS AND PATIENT COUNSELING

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ABSTRACT

Millions of people today use herbal therapies along with prescription and non prescription medications. Although considered natural, many of these herbal therapies can interact with other medications, causing either potentially dangerous side effects and / or reduced benefits from the medication. Currently, there is very little information published on herb-drug interactions whilst the use of herbs is progressively growing across the world. As there is large belief that herbal medicines are safe to use, it needs to be understood that depending on the amount and potency of the pharmacologic principles contained in the herbal preparation, potential exists for herb-drug interaction to occur when the herbal product is consumed with the modern day medicine. It should be understood that herbal preparations contain active phytochemicals in varying proportions which have a tendency like any other active pharmacological substance to alter the enzymatic systems, transporters and / or the physiologic process. The intent of this review is to update on some imminent issues that may arise if the modern medicine is mixed with a suspecting herbal preparation. These situations may arise in our daily lives due to the lack of strict adherence to regular drug prescription practices, unabated use of over the counter drug products and / or self prescription practices. Health-care practitioners should caution patients against mixing herbs and pharmaceutical drugs.

Keywords: Herb-Drug Interaction, Herbs, Counseling, Herbal Preparation

INTRODUCTION

Herbs have been used for medicinal purposes since the beginning of recorded time. Although most people believe that herbs are harmless plants, about one third of our drugs (including digitalis, morphine, atropine and several chemotherapeutic agents) were developed from plants. So, indeed, herbs can be potent products. Herbs can affect body functions; therefore, when herbs are taken concurrently with drugs, interactions are possible.

The increasing awareness of herbal medicines is acknowledged by World Health Organization (WHO). WHO has recently defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been in existence, almost for several hundreds of years, before the development and spread of modern medicine and still in use today. The traditional preparations comprise medicinal plants, minerals, organic

matter, etc. Herbal drugs constitute only those traditional medicines, which primarily use medicinal plant preparation for therapy. WHO estimates that about three quarters of world population currently use herbs and other forms of traditional medicines to treat their disease. Even as we entered into the new century with its exciting prospect of gene therapy, herbal medicines remain one of the common forms of therapy available to the world population.

Botanical medications have increased in popularity. In the United States, botanical products are now a \$1.5 billion per year industry. It is estimated that 60% to 70% of the American population is taking botanical products, but less than one third of these persons inform their medical practitioners of such use¹.

Today, our understanding of the interactions between drugs and herbs and between drugs

and food is still in its infancy. Much research is still required in herbal therapy to examine individual plant constituents and to determine how plants interact with drugs and food. Some researchers suggest that herb-drug interactions occur less often than predicted. If an interaction between an herb and a drug does occur, conventional drugs are usually the culprits because they are more pharmacologically active^{2,3}.

In this review an attempt has been made to update the most commonly occurring herb-drug interactions.

HERB-DRUG INTERACTIONS

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another. 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 e.g., herbs traditionally used to decrease glucose concentrations in diabetes could theoretically precipitate hypoglycaemia if taken in combination with conventional drugs. Because of the possible herb-drug interactions, health care providers need to be aware of herb and supplement use by their patients¹.

A drug interaction is defined as any modification caused by another exogenous chemical (drug, herb or food) in the diagnostic, therapeutic or other action of a drug in or on the body. The possibilities of drug interaction are endless, because more than 30000 over-the-counter products; more than 1000 unique chemical substances from which prescription drugs are produced; and hundreds of herbs, vitamins and minerals are available. The risk for drug interactions

increases with the number of products consumed e.g., for 2 products, the risk is 6%; for 5 products, 50%; and for 8 or more products, 100%⁴. The mechanisms for drug interaction can be divided into two general categories i.e. pharmacokinetics (absorption, distribution, metabolism, and excretion of a drug) and pharmacodynamic interactions (the combined pharmacological effects of a drug).

Pharmacokinetic interactions

Absorption

Herbs that have hydrocolloidal carbohydrate components such as gums and mucilage are soluble in water but poorly absorbable; examples include psyllium, rhubarb, flaxseed, marshmallow and aloe. These compounds bind to other drugs, particularly when consumed in their whole or powdered forms. For example, psyllium (an herb high in mucilage) inhibits the absorption of lithium. Rhubarb and aloe can cause diarrhea, which reduces the action of drugs that have a narrow therapeutic index (eg, digoxin, warfarin). In order to prevent an herb from binding with drugs, the drug should be taken 1 hour before or 2 hours after these herbal products.

Distribution

Herbs such as meadowsweet and black willow, which contain pain-reducing salicylates, may displace highly protein-bound drugs such as warfarin and carbamazepine thus increasing the adverse effects of these drugs. These products should not be taken concurrently^{2,3}.

Metabolism

Liquorice (as an herb, not a sweetener) decreases the metabolism of corticosteroids, leading to adverse and toxic effects from the buildup of corticosteroids. Recently, researchers discovered that St. John's wort

can induce hepatic microsomal enzymes in the cytochrome P-450 system; thus, it increases the metabolism of drugs metabolized in this system, such as digoxin and theophylline, protease inhibitors and cyclosporine. The drugs are thus rendered less effective, so concurrent use of liquorice with these drugs is not recommended^{2,3}.

Pharmacodynamic interactions

An example of a pharmacodynamic interaction is additive activity. For example, the hypnotic activity of benzodiazepines is increased by valerian and the anticoagulant action of warfarin is enhanced by ginkgo and possibly by many other herbs. It is best not to take these products concurrently³.

INTERACTION RISKS IN SPECIFIC PATIENT POPULATIONS

The following section reviews potential effects of dietary supplements in patients taking anticoagulants, cardiovascular medications, psychiatric medications, laxatives, diabetic medications or medications for human immunodeficiency virus (HIV) infection.

Patients receiving anticoagulants

Warfarin and other coumarin anticoagulants interact with many drugs, foods and medicinal herbs. Both garlic (*Allium sativum*) and ginkgo (*Ginkgo biloba*) interfere with platelet function in vitro and may increase the risk of bleeding when combined with warfarin. Garlic inhibits platelet aggregation and fibrinolytic activity in both patients with coronary artery disease and healthy subjects and has been associated with postoperative bleeding and spontaneous spinal epidural hematoma^{5,6}. In ginkgo, the constituent ginkgolides are potent antagonists of platelet activating factor.

Many medicinal herbs contain anticoagulant coumarins (not all coumarins are anticoagulant), which can also have additive effects when combined with pharmaceutical anticoagulants⁷. A Chinese herb, danshen (*Salvia miltiorrhiza*) has been associated with three cases of profound anticoagulation in patients on warfarin. Dong quai or danggui (*Angelica sinensis*, syn *A. polymorpha*), another Chinese herb, doubled prothrombin time (PT) and International Normalized Ratio (INR) in a 46-year-old African-American woman, previously stabilized on warfarin, who had ingested dong quai for four weeks. Laboratory values normalized within one month of discontinuing the herb⁸. In rabbits, dong quai extract affected neither baseline PT nor warfarin pharmacokinetics⁹. Given the case reports, however, caution would dictate that patients avoid combining dong quai with warfarin.

In one poorly documented case report, the anticoagulant effect of warfarin was potentiated by consuming an extract of the green fruit of papaya (*Carica papaya*)¹⁰. Green papayas, high in papain are commonly consumed in Southeast Asia. Although feverfew (*Tanacetum parthenium*) and ginger (*Zingiber officinale*) often are invoked as anticoagulant herbs in the literature, no cases of bleeding problems have been linked to these herbs. Although feverfew extracts and its sesquiterpene lactone constituents, notably parthenolide, inhibit platelet aggregation by inhibiting serotonin release, neither bleeding episodes nor abnormal coagulation tests have been reported. Although ginger inhibits platelet aggregation induced by arachidonic acid, epinephrine, adenosine diphosphate and collagen and a case report associated

consumption of a marmalade containing 15% raw ginger with inhibited platelet aggregation, clinical studies are reassuring¹¹⁻¹³. Case reports have shown interactions between the anticoagulant warfarin (Coumadin) and St. John's wort, ginkgo, garlic and ginseng^{14,15}. Studies have demonstrated that St. John's wort increases the metabolism of warfarin, leading to diminished serum levels¹⁶⁻¹⁹. However, the clinical response to the combination has not been quantified.

Ginkgo does not interact with warfarin or aspirin directly, but has demonstrated antiplatelet activity²⁰⁻²¹. In combination with nonsteroidal anti-inflammatory drugs, especially aspirin, ginkgo has been reported to cause severe bleeding, including intracranial bleeding²²⁻²⁴.

Garlic has intrinsic antiplatelet activity. However, one clinical trial has demonstrated that garlic is safe and without any serious hemorrhagic risk for monitored patients taking warfarin²⁵.

A low-quality clinical study found no effect of Asian ginseng (*Panax ginseng*) in combination with warfarin¹⁶. American ginseng (*Panax quinquefolius*), a separate plant, decreases warfarin serum levels in humans, resulting in less anticoagulation²⁶. Eleuthero (*Eleutherococcus senticosus*) has not been studied; however, it contains a constituent that inhibits platelet aggregation.

The narrow therapeutic index of warfarin and the serious consequences associated with small changes, the anticoagulation status in patients taking dietary supplements should be carefully monitored whenever they initiate or stop taking any supplement or when a new bottle of the same product is used, until the effect in the individual patient is known.

Specifically, patients receiving American ginseng should be monitored when changing products or even bottles of the same product²⁷.

Patients receiving cardiovascular medications

Of all the supplements used by patients who have cardiac disease, St. John's wort, used to treat mood disorders, is associated with the most interactions. It decreases serum levels of verapamil and statins^{21,22,28}. Blood pressure and lipid levels, respectively, should be monitored closely if a patient is taking one of these drugs and St. John's wort.

The suspected mechanisms of St. John's wort interactions are by the induction of cytochrome P450 (CYP450) isoenzymes CYP3A4, CYP2C9, CYP1A2 and the transport protein P-glycoprotein, leading to decreased concentration of medications¹⁸. In one study, St. John's wort decreased digoxin blood levels by 25 percent, most likely by inducing the P-glycoprotein, which decreases the bioavailability of digoxin^{29,30}. Ginseng is another commonly used herb that has been reported to cause an increase in digoxin serum levels in a case report of one patient³¹. Digoxin levels should be monitored in patients taking eleuthero or St. John's wort.

Consuming yohimbe (*Pausinystalia yohimbe*) bark or extract increases the risk of hypertension. The constituent alkaloid, yohimbine (used conventionally to treat erectile dysfunction), increases blood pressure more in hypertensive than in normotensive subjects³². Hypertensive effects are potentiated when yohimbine is combined with tricyclic antidepressants³³. Foxglove (*Digitalis purpurea*) and other herbs contain cardiac glycosides that could

have an additive effect with digitaloid cardiac glycosides³⁴ but these are not commonly used medicinal herbs. The only reported case of an herb-drug interaction associated with digitalis proved to interfere between a preparation purported to contain Siberian ginseng (eleuthero) (*Eleutherococcus senticosus*) and the digoxin assay, causing spuriously elevated digoxin levels³¹.

Patients receiving psychiatric medications

St. John's wort may have an effect on serotonin levels. It has been associated with serotonin syndrome in patients also receiving a selective serotonin reuptake inhibitor (SSRI).³⁵ St. John's wort should be tapered off when an SSRI is initiated³⁶. Patients should be cautioned not to initiate St. John's wort when receiving these drugs.

St. John's wort decreases serum levels of psychiatric medications metabolized by the CYP450 enzyme system. It has been shown to affect serum levels of benzodiazepines and tricyclic antidepressants, although these changes may not result in a clinical effect³⁷⁻³⁹.

Patients taking bulk laxatives

Psyllium and related bulk-forming laxatives are dietary supplements often not considered to be medications by many patients. However, they can slow or diminish absorption of many drugs. Psyllium can reduce carbamazepine absorption and serum levels⁴⁰. Additionally, there is a case report showing that psyllium decreased the absorption of lithium⁴¹. As a general rule, bulk laxatives such as psyllium should not be taken at the same time as other medications; their use should be separated by several hours to allow absorption to occur.

Bulk-forming laxative herbs, such as the hydrocolloidal-fiber-containing guar gum

(*Cyamopsis tetragonolobus*), psyllium (*Plantago* spp.), konjac (*Amorphophallus rivieri*) and others, taken in sufficient quantity can delay gastric emptying and reduce the rate of absorption of carbohydrates and drugs, including lithium, glibenclamide, lovastatin, tricyclics and digoxin⁴¹⁻⁴⁵. Laxative herbs that contain stimulant anthranoids, including senna species (*Cassia senna*, *C. acutifolia*, and *C. angustifolia*), Chinese rhubarb (*Rheum officinale*), cascara sagrada (*Rhamnus purshiana*), frangula or alder buckthorn (*Rhamnus frangula*), yellow dock (*Rumex crispus*) and aloe, the leaf exudate of *Aloe vera*, can decrease the absorption of intestinally absorbed drugs due to an increased rate of intestinal transit⁴⁶.

Patients receiving diabetes medications

Glucose control in both insulin-dependent (type 1) and non-insulin dependent (type 2) diabetics can be affected by consumption of hypoglycemic herbs.

More than 400 plants have been traditionally used for their hypoglycemic action;⁴⁷ of these, *Aloe vera*, syn. *A. barbadensis*, leaf juice;⁴⁸ the fruit of bitter melon/karela (*Momordica charantia*) (found to improve glucose tolerance without increasing insulin levels);^{49,50} and the seeds of fenugreek (*Trigonella foenum-graecum*),⁵¹ are commonly used herbs with documented hypoglycemic effects. Also, two clinical studies with a water-soluble acidic fraction of an ethanol extract of gurmar (*Gymnema sylvestre*) leaves have reportedly reduced insulin requirements in both insulin-dependent and non-insulin-dependent diabetics, effects comparable to those observed with *Aloe vera* juice and glibenclamide.⁵²⁻⁵⁴ Antidiabetic effect of

fenugreek is attributed to intestinal effects of the gum fiber (galactomannans), which also displays hypocholesterolemic activity⁵¹.

Ginseng has hypoglycemic activity in patients with diabetes and this effect might be additive in patients taking oral hypoglycemics or insulin. Chromium and psyllium also have hypoglycemic effects⁵⁵⁻⁵⁷. The effect of these supplements is unpredictable in individuals and no specific changes in hypoglycemic doses are needed unless blood glucose changes occur.

While additive effects are certainly possible when these herbs are combined with the hypoglycemic drugs, appropriate self-monitoring by the patient and clear lines of communication between the patient and health care practitioner should avert problems.

Patients receiving hiv medications

Most antiretrovirals are metabolized via the CYP3A4 and P-glycoprotein systems. Dietary supplements that induce these systems may decrease serum levels of the antiretrovirals. St. John's wort is the dietary supplement with the most evidence of an effect on these systems⁵⁸. Limited clinical research has demonstrated reductions in antiretroviral serum concentrations in patients taking garlic and vitamin C^{59, 60}. Milk thistle, *Echinacea* species, and goldenseal inhibit CYP450 enzymes in vitro, but not to a clinically relevant effect^{58, 61}. The effectiveness of HIV therapy should be monitored in patients taking these supplements, particularly St. John's wort. Because of the risk of a dangerous interaction, patients taking antiretrovirals should be discouraged from using St. John's wort.

PATIENTS COUNSELING ABOUT HERB-DRUG INTERACTIONS

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)⁶². A survey of 515 users of herbal remedies in the UK found that 26% would consult their general practitioner for a serious adverse drug reaction associated with a conventional over-the-counter medicine, but not for a similar reaction to a herbal remedy⁶³. Patients may not be forthcoming about the use of herbal medicine even if it causes severe adverse effects because they fear censure. Clinicians must ask patients about their use of herbs in a non-judgmental, relaxed way. A disapproving manner will ensure only that a patient will conceal further use. The patient should be treated as a partner in watching out for adverse reactions or interactions and should be told about the lack of information on interactions and the need for open communication about the use of herbal remedies.

Formulation, brand, dose and reason for use of herbs should be documented on the patient's charts and updated regularly. Any laxative or bulk-forming agents will speed intestinal transit and thus may interfere with the absorption of almost any intestinally absorbed drug⁶⁴. The most popular stimulant laxative herbs are the anthranoid-containing senna (*Cassia senna* and *C. angustifolia*) and cascara sagrada (*Rhamnus purshiana*).

Dried exudate from the aloe vera (*Aloe barbadensis*) leaf (not gel) also contains anthranoids and is used as a laxative. Aloe vera gel, found within the leaves, is used topically for burns and cuts and is sometimes recommended by herbalists for internal ingestion to treat ulcers and other disorders. The gel (or juice made from the gel) does not contain anthranoids, but some oral preparations are contaminated by the laxative leaf. Less commonly used anthranoid-containing plants are frangula (*Rhamnus frangula*), yellow dock (*Rumex crispus*) and Chinese rhubarb (*Rheum officinale*). Patients with clotting disorders, those awaiting surgery or those on anticoagulant therapy should be warned against the concurrent use of ginkgo, danshen, dong quai, papaya or garlic. Although the combined use of anticoagulants with these herbs should be discouraged, patients who insist on the combination should have their bleeding times monitored (most of these herbs interfere with platelet function, not the coagulation cascade and thus will not affect prothrombin time, partial thromboplastin time, or international normalised ratio [INR]). Many other herbs also contain anticoagulant substances; as a precaution, patients on warfarin should have an INR measurement within a week of starting any herbal treatment. Patients on serotonin-reuptake inhibitors, cyclosporin, digoxin, phenprocoumon or any critical chronic medication should avoid St John's wort; those on phenelzine should avoid ginseng and those on tricyclic antidepressants should avoid yohimbine. Patients taking phenytoin should avoid Ayurvedic herbal mixtures for seizures. Liquorice (a very common ingredient in Chinese herb mixtures)

may potentiate the action of corticosteroids, and betel nuts have pronounced cholinergic effects. There are doubtless many as yet undiscovered interactions.

CONCLUSION

All drugs with a narrow therapeutic index may either have increased adverse effects or be less effective when used in conjunction with herbal products. More research is required to define the interactions. When adverse reactions are experienced with drug therapy, patients must always be queried as to their intake of herbal products e.g., what they are taking in pills and tincture form, what they are drinking as teas, and what food they are eating^{65, 66}.

Patients taking drugs with a narrow therapeutic index (cyclosporine, digoxin, hypoglycemic agents, lithium, phenytoin, procainamide, theophylline, tricyclic antidepressants and warfarin) should be discouraged from using herbal products.^{2, 65}

Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. Plausible cases of herb-drug interactions include bleeding when warfarin is combined with ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), dong quai (*Angelica sinensis*) or danshen (*Salvia miltiorrhiza*); mild serotonin syndrome in patients who mix St John's wort (*Hypericum perforatum*) with serotonin-reuptake inhibitors; decreased bioavailability of digoxin, theophylline, cyclosporin, and phenprocoumon when these drugs are combined with St John's wort; induction of mania in depressed patients who mix antidepressants and *Panax ginseng*; exacerbation of extrapyramidal effects with neuroleptic drugs and betel nut (*Areca catechu*); increased risk of hypertension when

tricyclic antidepressants are combined with yohimbine (*Pausinystalia yohimbe*); potentiation of oral and topical corticosteroids by liquorice (*Glycyrrhiza glabra*); decreased blood concentrations of prednisolone when taken with the Chinese herbal product xiao chai hu tang (sho-saiko-to); and decreased concentrations of phenytoin when combined with the Ayurvedic syrup shankhapushpi. Anthranoid-containing plants {including senna (*Cassia senna*) and cascara (*Rhamnus purshiana*)} and soluble fibres (including guar gum and psyllium) can decrease the absorption of drugs. Many reports of herb-drug interactions are sketchy and lack laboratory analysis of suspected preparations. Health-care practitioners should caution patients against mixing herbs and pharmaceutical drugs. Because physicians are likely to encounter patients who are using herbal remedies, they need to be aware of the purported effects of these products. They also need to be cognizant of the adverse effects of herbal remedies and the possibility of deleterious drug interactions.

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