

Herb-Drug Interactions

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Abstract

Herbal medicinal products (HMPs) are widely used all over the world because of their ready availability, consideration as safe to use and lack of medical consultation. But, it is proved that interaction can occur between HMPs with western medicine, other HMPs, alcohol and food. It should be noted that not all HMPs can interact with western medicines and vice versa and the interaction may be synergistic or antagonistic. So, health care professionals and pharmacists have to play an important role in giving advisory knowledge on and monitoring concurrent use of herbal and conventional medicines and to collect the data for suspected herb drug interactions.

Key words: Drug interactions, Herbal drugs, Pharmacokinetics, Pharmacodynamics.

INTRODUCTION

It is a common belief amongst people and health professionals that anything natural in the world is safe. In fact, it is far away from the truth. As per recent survey, many people consume HMPs without consulting their physicians¹ and it is the reason for enhancement of extent of herb drug interactions. An estimated 5-20 % of general people consume HMPs costing US \$ 60 billion². The interaction between herb and drug may lead to enhancement or reduction in metabolizing enzyme activity leading to unexpected concentration of the therapeutic drug and further, incorrect laboratory reports and confusion in proper diagnosis of the disease. Development of public interest in HMPs is because of their natural origin³.

US FDA suggests that medicines have to be proven to be safe before being released in the market. But HMPs do not fall in drug category until they are marketed for treatment of any disease. In UK, products having license as a medicinal product by Medicine Control Agency (MCA) are treated as food and no health claim can be made on label which may not exactly reflect the content⁴. In this review, the issue that herb can interact with drugs leading to hazardous health effects and all natural entities may not be safe has been addressed

When HMPs and western drugs are administered together, then they may interact with each other in the body leading to alterations in the kinetics and dynamics of HMPs and / or the drug. Such interactions are called as herb-drug interactions.

As stated, herb drug interactions (HDIs) can impact effectiveness of treatment and health. There are several effects that can occur because of HDIs such as enhancement of therapeutic effect of drugs may lead to either over dosage or decrease in therapeutic effect of drug leading to treatment failure / drug resistance. This limits further options of treatment, modification of drug effect leading to unusual complications, increase in side effects of drug leading to toxicity. This article deals with only herbal and western medicine interactions.

MECHANISMS OF HDIs

Like conventional drug interactions, some HDIs are very specific and may be classified as pharmacokinetic HDIs (HMP and /or drug affects absorption, distribution, metabolism, excretion of each other) and pharmacodynamic HDIs (HMP and /or drug changes the effects of each other at the site of action)⁵. So like conventional medicines, kinetics of herbal drugs can be influenced by factors such as genetics, age and cigarette smoking⁶

1. Pharmacokinetic interactions

These interactions modify the pathways of herb and drug in the body so that changes in the concentration of either of one get affected. If this leads to enhancement of drug concentration in the body, then side effects and / or toxicity of drug can occur while reduced drug concentration leads to treatment failure or development of drug resistance. These interactions mainly occur in GIT, kidney and liver. In GIT, some herbs alter atmosphere of stomach probably by changing stomach pH. Due to reduction in pH, some drug may remain in the stomach in spite of entry in blood circulation. Some herbs

may enhance the digestive process of the drug causing reduction in time of drug to be absorbed by stomach e.g. laxatives. Liver is responsible for first pass metabolism⁷ so liver has a major role in controlling blood drug levels. Some herbs may inhibit or induce liver enzymes and may decrease or increase bioavailability of a drug. This frequently happens on co-administration of herbs and antiretroviral e.g. St. John's Wort activates CYP p450 and decrease peak digoxin concentration⁸ by 30 % and kava-kava inhibits cytochrome p450 and cause disorientation in patients taking Alprazolam⁹. Kidney is responsible for elimination of drugs. So herbs causing damage to kidney may increase the drug level and herbs favoring kidney function may decrease the drug concentration. Pharmacokinetic interactions are difficult to predict.

2. HMPs are not subjected to quality assurance for purity and potency, so that contents of HMPs may vary from batch to batch or in the same batch.
3. There is no advancement in research on HMPs as compared to research on synthetic drugs.

PHARMACIST ROLE IN HDI

One of the ways of preventing complications with HDIs is pharmacist's intervention, who is a part of professional health care system and can play an important role in advising, monitoring and reporting HDIs. Therefore, pharmacists should ask the patients taking western medicines about their use of HMPs and vice versa and maintain the record appropriately. MCA recognize that pharmacists can play a role in identifying HDIs. For this purpose, they advise to maintain yellow card report in which pharmacist encouraged to report suspected HDIs

Table No 1. Potential pharmacodynamic interactions

Sr. No.	Herbal Phytoconstituent	Drug	Dynamism	Reason
1	Panax ginseng	Antidiabetics	Potentialiation	Hypoglycemic activity
2	Aloes and Senna	Antidiarrhoeals	Antagonism	Laxatives
3	Dandelion	Diuretics	Potentialiation	Diuretic
4	Ginger, Garlic	Warfarin	Potentialiation	Antiplatelet action ¹¹
5	Prime rose oil	Anticonvulsants	Antagonism	Lowering of seizure threshold ^{12,13}
6	Liquorice	Hypertensive	Antagonism	Increase in BP and Hypokalemia ¹⁴
7	Chaparral	Methotrexate	Potentialiation	Anticancer action

2. Pharmacodynamic interactions:-

They are related to action of herb and drug, depending on nature of phytochemical constituents of herbs, their pharmacology and pharmacology of the drug used simultaneously. These interactions can be predicted. If a herb and a drug are taken together, then they may work together (synergism) leading to enhancement of each other's pharmacological action or they may oppose each other (antagonism) leading to decrease in each other's pharmacological actions¹⁰.

REASONS FOR HDI

Unfortunately, the frequency of HDIs is increasing probably because of lack of knowledge regarding HDIs. Reasons for this include -

1. Many Clinicians do not have adequate knowledge of consequences of combinations of herbs and drugs.

for licensed and non-licensed HMPs. Remaining essential components of yellow card system are patient's details, reporter's details, route, dosage, reason for use, outcome, manufacturer's name, batch number, type of extract, Latin binomial name and plant part used.

OTHER WAYS TO AVOID HDIs

A) Following are 10 tips to avoid HDIs according to Glenda Meneilly, Pharmacist at Oak Tree Clinic, in British Columbia Persons with AIDS Society which are applicable for treatment of AIDS along with herbal drugs¹⁵-

1. Knowledge is power

Knowledge is your best defense against drug-herb and herb-herb interactions. Know what you are taking and why? Your alternative and conventional medical providers should provide you with names of all the

drugs and herbs, the reason for taking them, the expected benefit and potential side effects. Avoid anything that has a "secret formula". If it works, there should be evidence that it does. Unfortunately, lack of knowledge about how medicinal plants and pharmaceutical drugs affect each other and large variations between individuals make identifying adverse drug-herb interactions difficult. One of the key things you can do is to be proactive and work closely with your doctor, pharmacists and complementary care practitioners to make sure that each of them are aware of all the substances you are taking and to ensure you get the information you need to make informed treatment decisions.

2. Your Pharmacist is your friend

Make all your health practitioners aware of everything you are taking. Project Inform suggests the "Brown Bag Medicine Check Up". Put all of your medications, including over-the-counter, prescription and complimentary products like herbs and vitamins in a bag and take them to your various health care providers so that they can conduct a personalized review. Typing a list of all the supplements and herbs you take and providing that to your health care providers for your file can be helpful. New information on benefits, adverse effects and drug interactions with herbal remedies is being published in the medical and Pharmaceutical literature all the time- your pharmacist or physician may be able to tell you of recent developments (or you may be able to tell them). Whichever way, you'll all be better off.

3. Buyer beware

Buy your herbal products from a reputable manufacturer or a store that has been in business for some time. Ask your alternative medical provider to recommend a good source of high quality herbs. Products from less reputable manufacturers may be mislabeled, have variable (or incorrect) herb content or quality, or be contaminated with other ingredients. You can't predict or evaluate a drug interaction if you don't know what's in the product.

4. One thing at a time

Start one product at a time and don't use in larger than recommended doses. Avoid combination products with a long list of ingredients. In general, don't start a new herbal regimen at the same time as you start a new antiretroviral regimen - wait until you are stabilized on your new HIV medications. There may be times when you will choose to take herbs to alleviate some of the short-term side effects of a new regimen, such as ginger for nausea, or raspberry tea for diarrhea.

5. Watch the kids

Use herbal products in children or infants only under the

care of a trained practitioner. Children are more likely to have adverse effects due to altered metabolism. Avoid herbal treatments if you are pregnant or planning a pregnancy. Some herbs like feverfew and goldenseal can cause premature labour, others such as hawthorn and kava-kava decrease the tone of the uterus.

6. Write it down

Keep a diary of your response to each treatment you try and don't continue use for more than a few weeks if you are not achieving the desired benefit. There are very few long-term studies on most herbal remedies. Minimizing the number of herbs taken decreases the chance of interaction.

7. Timing is important

Because, we have limited information of drug-herb interactions due to altered absorption, try to separate your doses of antiretrovirals and herbs/supplements by at least an hour. This is especially important for drugs with food restrictions such as didanosine (DDI) and indinavir (Crixivan) or those sensitive to changes in stomach pH, such as itraconazole and ketoconazole.

8. Have a healthy respect for nature

Just because it's natural doesn't mean it's harmless. Many people assume that because they are taking a "natural" product that there are no potential adverse effects and that dosing recommendations are to be ignored. There are a wide variety of toxic effects of herbs. Avoid taking herbs that have known toxic effects, such as pennyroyal, comfrey, germander and life root. HIV infected persons should avoid the long-term use of Echinacea as it may increase the rate of replication of the HIV virus.

9. An ounce of prevention

Be especially careful when adding herbal treatments if you are on medication for the treatment of other chronic medical conditions such as: high blood pressure, high cholesterol or triglycerides, diabetes, heart failure or rhythm disturbances, seizure disorders, Parkinson's disease, rheumatoid arthritis, gout, or cancer chemotherapy. Be really, really careful if you are taking blood thinners such as warfarin (Coumadin). Some herbs can increase the toxicity of drugs used to treat these conditions or counteract their effectiveness. Examples include: Ayurvedic Shankapushpi can decrease the effectiveness of phenytoin in the treatment of seizures, wormwood can lower seizure threshold, black cohosh can antagonize the effects of some high blood pressure medications, figwort can increase possibility of side effects to digoxin, red clover, chamomile and many others can affect anticoagulants.

10. Use common sense

If something seems too good to be true, it usually is. The most expensive products are not always the best. No drug or herb has "no known side effects". Follow directions - if you are boiling herbs in water (making a decoction) or making teas (infusions) follow measurement and preparation instructions carefully.

B) Questionnaire for patients

Asking the following questions to patients taking herbal medicines, will also help to reduce consequences of HDIs

1. Are you taking herbal medicinal products?
2. Are you allergic to any herbal product, herbal supplement / natural remedy?

3. How long you are using HMPs?

4. Are you taking any prescription or non-prescription medication for treatment as the herbal products?

5. Have you used same herbal product as before?

6. If female, are you pregnant or breast feeding?

USE OF HMP'S BEFORE / DURING / AFTER THE SURGERY

HMPs have tremendous potential to interact with anesthetics so it is advisable to discontinue the use of HMPs before/during/after the surgery in order to prevent complicated and delayed outcome¹⁶. According to pharmacokinetics of HMP constituents, following is minimum period for discontinuation of herbal drugs¹⁷.

Table No 2. Minimum period for discontinuation of herbal drugs

Sl. No.	Herbal drug to be discontinued	Period of discontinuation	Otherwise leads to
1	Garlic and Ginseng	7 days	Severe bleeding
2	Gingko biloba	3 days	Bleeding as it inhibit platelet aggregation
3	Kava-kava	20 hrs	CNS depression as it increases sedative effect of anesthetics
4	Ma-huang	20 hrs	Increase in BP and heart rate

Table No 3. Following chart shows various important HDIs

Sr. No.	Herbal drug	Western Drug	Outcome of interaction or fate of western drug
1	St. John's Wort	Antiretrovirals	Treatment failure ¹⁸
2	Ginkgo biloba	Warfarin	Hemorrhage ¹⁹
3	Danshen	Warfarin	Increased bioavailability ²⁰
4	Garlic	Sequinavir	MDR-1 gene activation
5	Echinacea	Methotrexate	Liver inflammation
6	Valerian	Anesthetics	Prolongation of effect ²¹
7	Grape fruits	Ca-channel blockers	Increased AUC curve
8	Vitamins	Antipyrene	Enhanced oxidation ²²
9	Vitamins	Phenacetin	Increased metabolism ²²
10	Citrus fruits	Cyclosporine	Increased absorption and acute toxicity ²³
11	Colchicines	Simvastatin	Acute myopathy ²⁴
12	Garlic	Ritonavir	Decreased AUC ²⁵
13	Ginkgo biloba	Diltiazem	Increased bioavailability ²⁶
14	Grape fruits	Fexofenadine	Increased bioavailability ²⁷
15	Grape fruits	Sildenafil citrate	Increased bioavailability and delayed absorption ²⁸
16	Piperine	Propranolol, Theophylline	Increased C _{max} and AUC ²⁹
17	St. John's Wort	Antiasthmatics	Decreased effectiveness
18	Feverfew	Anticoagulants	Bleeding
19	Goldenseal	Hypotensives	High B.P.

CONCLUSION

Herbal medicines can cause severe drug interactions, toxic effects and also morbidity and mortality. Even though HMPs are available without prescription, medical advice is very important and health care professionals should be aware of latest and possible options for therapeutic management. From this, it is clear that general consideration that herbal products can be given to the bed ridden patients or post operative patients is totally incorrect. So it is very necessary to maintain the permanent record of HDI whenever it is happened, as a case study, so it can be used as a ready reference in order to avoid further hazardous consequences.

This article is not a debate against HMPs. All over the world, HMPs has resurgence and we should acknowledge their effectiveness, but it is meant for creation of awareness in between medical practitioners especially for those who are having scarcity about information regarding use of HMPs by patients and complications associated with them.

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