INTERACTIONS BETWEEN HERBAL REMEDIES AND MEDICINAL DRUGS - CONSIDERATIONS ABOUT CUBA

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SUMMARY

The use of herbal products to treat a wide range of conditions is rapidly leading to increased intake of phytochemicals. This is one of the main reasons for reinforcing the surveillance of the safety, efficacy and quality control of traditional and complementary medicines. Herbal preparations can interact with a drug at pharmacokinetic, pharmacodynamic and pharmacogenetic levels. In this article interactions between herbal products and conventional medicines are reviewed. Reports about side effects of traditional medicines and main interactions between herbal medicines and conventional drugs in Cuba are also included. Herbal products are currently not subject to the rigorous testing indispensable for conventional drugs. However, if potential drug interactions are to be predicted, it is essential that the ability of herbal products to interfere with drug-metabolizing enzyme systems is fully established.

KEY WORDS

drug interactions, herbal-drug interaction, pharmacovigilance, Cuba

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INTRODUCTION

The use of herbal medicines has become increasingly popular throughout the world. In addition, many patients are now taking herbal medicines in combination with conventional drugs /1,2/. The combination of herbal and conventional medicines may cause herb-drug interactions, some of which may cause serious side effects, particularly in patients with cancer and HIV/AIDS /3/. Interactions between herbs and drugs can be identified in a variety of ways. Case reports and spontaneous reporting provide important sources of information and a number of these have been reviewed recently /4/.

A more systematic approach for identifying herb-drug interactions is clearly desirable. At present there is no regulatory requirement to study herb-drug interactions and interactions for specific herbal products are generally not known or are poorly studied /5/. Thus, for public safety there is a need to carefully study herb-drug interactions, especially for commonly used herbal products.

The objective of this review is to provide updated information on the interactions between herbal and synthetic medicines and their mechanism of action and to show the main examples of interactions between herbal medicines and drugs in Cuba.

HERBAL REMEDIES

During the last decade, an explosion in the consumption of herbal remedies especially among older people has been witnessed in North America and Europe, particularly in Germany, which leads the world in the sale of such remedies, followed by France /6/. A major cause of current concern is that herbal remedies may interact with medicinal drugs, altering the pharmacokinetic characteristics of the latter to clinically significant interactions. Herbal medications are taken not only by healthy persons who want to protect themselves from the onset of disease or to improve their well being, but also by patients suffering from life-threatening conditions who simultaneously receive one or more medicinal drugs /7,8/.

The theoretical 'interactions' are based on the effect of herbal products. For example, echinacea may "interfere with immuno-suppressive therapy" /9/, saw palmetto may "interfere with existing hormone therapy" /10/, and "valerian could increase the sedative

effects of anesthetics" /11/. However, 'there is no evidence of interactions among echinacea, valerian and saw palmetto and conventional treatments" /12/.

The metabolism of a drug can be altered by another drug or foreign chemical and such interactions can often be clinically significant. The herbal preparations may interact with a drug at pharmacokinetic and pharmacodynamic levels at the site of absorption. This reduces the amount of drug absorbed or its rate of absorption, thus modifying the pharmacological effect of the drug. Changes in absorption are usually a reduction rather than an increase, although the opposite can occur. The factors affecting drug absorption are intestinal pH, complex formation, alterations in gastrointestinal motility. Herbal preparations may inhibit drug absorption as a result of tannins and polyphenols forming complexes with drugs. In practice, this may not be significant, as tea contains tannins and polyphenols, and tea is used by patients to help swallow tablets, but does not appear to render many drugs inactive /13,14/.

Herbal medicines studied for drug interactions include St John's wort (*Hypericum perforatum*), *Ginkgo biloba*, *Panax ginseng*, kava, garlic, valerian and tea, among others /15/. The best example of an interaction at the pharmacokinetic level is the interaction that involves cytochrome P450 enzymes (Table 1).

TABLE 1

Known and possible herb-drug interactions attributed to effects of cytochrome P450 /20/

Herb	Drug	Known or possible effect	CYP enzyme involved
St. John's wort (*Hypericum perforatum*)	Cyclosporin	Organ rejection during transplant (decreased cyclosporin levels)	CYP 3A4 induction
Garlic (*Allium sativum*)	Saquinavir	Drug bioavailability decrease	Gut CYP3A4 induction
Ginseng (*Panax ginseng*)	Phenelzine	Mania induction	CYP 2E1 inhibition

Cytochrome P450 (CYP) enzymes, a superfamily of enzymes found mainly in the liver, are involved in the metabolism of a plethora of xenobiotics and have been shown to be involved in numerous interactions between drugs, foods and herbs. They play a key role in the oxidation of xenobiotics and endogenous compounds. If CYP enzymes are induced, some drugs will also be metabolized faster. Inhibition of the CYP catalyzed metabolism of a drug by herbal preparations will result in an elevation of its concentration in tissues, which could lead to various side effects, particularly for drugs with a low therapeutic index /16,17/.

The induction or inhibition of a CYP enzyme isoform responsible for the metabolism of a drug can reduce or increase its expected therapeutic capacity by altering plasma drug levels /18,19/.

Transporter-based interactions have been increasingly documented. Various reported mechanisms of interaction, such as enzyme inhibition/induction, may be due in part to the inhibition or induction of transport proteins such as P-glycoprotein (P-gp), organic anion transporter (OAT) or organic anion transporting polypeptide (OATP) /20/.

The main transporter involved in herbal drug interaction is P-glycoprotein; this is a 'pump' found in cell membranes (gut, blood-brain barrier, etc.), which affects serum drug levels by blocking or facilitating entry into cells. This pump can even eject drugs from the gut lining that have already been absorbed /21/.

Drugs which have been affected by P-glycoprotein include cyclosporin, tamoxifen, paclitaxel, saquinavir, and digoxin, among others. One example is digoxin interacting with St. John's wort, one of the most commonly used herbal antidepressants for the treatment of minor to moderate depression. In this case, St. John's wort induced P-glycoprotein and digoxin is a substrate for P-glycoprotein, thus the efficacy of digoxin was decreased /22,23/.

Pharmacodynamic interactions involving herbs are considered additive, synergistic or antagonistic, effects possible for combinations of any type of drug including herbs. Herbal sedatives, anticoagulants, anti-hypertensives and others *might* increase the activity of a concurrent drug taken for the same purpose /24/.

Valerian, a common herb used as a sedative, is another example of this interaction because it inhibits the breakdown of GABA and enhances benzodiazepine binding. It could also increase the

pharmacological effectiveness of carbamazepine. Another example is passion flower which contains chrysin, a partial agonist of the benzodiazepine receptor, that shows anti-seizure effects in mice, but the activity of flavonoids is weak compared to synthetic drugs /25/.

Nowadays, genetic polymorphisms are important in determining interindividual and interethnic differences in drug disposition and response that may also influence drug-drug and herb-drug interactions. There are more than 57 active human CYP genes and 58 pseudogenes that are known, and the majority of the genes are polymorphic. Likewise, there is considerable genetic diversity in more than 600 transporters belong to the two major families of membrane transporters, the adenosine trisphosphate-binding cascade (ABC) transporters and the solute carrier (SLC) transporter /26-28/.

POSSIBLE UTILITY OF A PHARMACOGENETIC APPROACH IN HERB-DRUG INTERACTIONS

Not only pharmacokinetics and pharmacodynamics are involved in the interactions of herbs and drug. Nowadays, the polymorphisms in the genes for the drug-metabolizing enzymes and transporters are involved in many herb-drug interactions. Currently, the pharmacogenetics approach has been used mainly to study drug-drug interactions so there is considerable potential to extend this to the study of herb-drug interactions *in vivo*. Genetic polymorphisms are important in determining interindividual and interethnic differences in drug disposition and response and may also influence drug-drug and herb-drug interactions /29,30/.

For example, *Ginkgo biloba* and omeprazole interactions have been described. Ginkgo is one of the most widely used herbal products in the world and omeprazole, a widely used proton pump inhibitor, is a well known CYP2C19 substrate. Recent studies have revealed that *Ginkgo biloba* can induce omeprazole hydroxylation in a CYP2C19 genotype-dependent manner. This concurrently decreases the renal clearance of 5-hydroxyomeprazole. Other CYP2C19 substrates may also significantly decrease omeprazole effectiveness. Some major drugs that are metabolized by hydroxylation include the protease inhibitor nelfinavir; tricyclic antidepressants (imipramine, amitriptyline, clomipramine), benzodiazepines (diazepam, flunitrazepam); proguanil and other proton pump inhibitors (lansoprazole, panto-

prazole). Potential interactions of *G biloba* with these drugs should be kept in mind as these drugs are more likely to be taken by elderly patients in conjunction with *G. biloba* /31/.

In general, interactions between herbs and drugs are based on a mutual relation of all the factors mentioned above including pharmacokinetic, pharmacodynamic, and pharmacogenetic properties.

CONSIDERATIONS ABOUT CUBA

Cuba has a long tradition of using medicinal plants since Spanish colonization. Traditional medicine is both recognized and integrated into the National System of Health in the 1990s /32/. Most people believe in the properties of traditional medicine. Cuba possesses a strategy for the development of natural products in order to fulfil WHO guidelines /33/. Some of the herbal medicines most used in Cuba are calendula tincture (*Calendula officinalis*), ginger extract (*Zingiber officinales* L.), onion cream (*Alliun cepae* L.), and anamu cream (*Petiveria alliacea* L.). These products are included in the Therapeutic Guide of Phytomedicines from the Ministry of Public Health of Cuba /34/. There are other Cuban phytomedicines that have been well researched, such as Vimang®. This is extracted from the stem bark of *Mangifera indica* and has been used to treat various pathologies /35/. CIKRON-H from *Rhizophora mangle* is used for healing /36/ and ateromixol (mixture of policosanols) from sugar cane wax has been registered as a hypocholesterolemic agent /37/.

The regulatory status of herbal products differs significantly from country to country. Currently fewer than 70 countries regulate herbal medicines and few countries have systems in place for the regulation of traditional health practitioners /38,39/.

Cuba has a National Regulatory Authority with a defined policy about the regulation of traditional medicine, which demands that information about the interactions between natural products and conventional drugs should be reported. Moreover, Cuba has a center in charge of pharmacovigilance for the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. It includes herbal, traditional and complementary medicines, blood products, biological medical devices and vaccines /32/.

TABLE 2

Main herbal products with drugs in database, Cuba (2003-first semester 2007) /43/

Herbal remedies	Drug	Adverse effect
Extract of aloe (*Aloe vera* L.)	Clortalidona	Rash
	Morphine	Nausea
	Erythromycin	Feeling down
	Hydrochlorotiazide	Paresthesia
	Enalapril	Low blood pressure
	Captopril	Low blood pressure
	Ateromixol	Epigastric disorders
	Aspirin	Bruising
	Ateromixol	Epigastric disorders
Caña santa (*Cymbopogon citrates*)	Captopril, clortalidona	Redness
	Captopril	Low blood pressure
Guava (*Psidium guava* L.)	Kanamicyn, multivitamins	Epigastric disorders
Llantén	Manzanilla	Gingivitis
	Tilo	Rash
	Isosorbide dinitrate, clortalidona, enalapril	Edema of glottis
Menta	Salbutamol	Rash
	Clortalidona	Insomnia
Noni (*Morinda citrifolia*)	Warfarin, nitropental	Gingival bleeding
Vimang (*Manguifera indica*)	Ibuprofen	Dizziness, redness
	Captopril	Dizziness
	Salbutamol spray	High blood pressure

TABLE 3

Examples of interactions common in Cuba between herbal products and conventional drugs, and their proposed mechanism /44/

Herbal remedy	Conventional drug	Adverse effect	Proposed mechanism
Imefasma - a syrup very common in Cuba used for grippe (mixture of banana stem, flower of *Hibiscus elatus*, *Aloe vera* L., orange and propolis)	Digoxin, captopril	Diarrhea	Sabila (*Hibiscus elatus*) has laxative properties; its use causes depletion of potassium and consequently induces diarrhea.
Caña Santa *Cymbopogon citratus*	Captopril, clortalidona	Redness, blush	This herbal medicine interacts with diuretics and angiotensin converting enzyme inhibitors. Also produces vasodilatation and consequently redness and blushing.
Guava *Psidium guajava* L.	Multivitamins	Epigastric disorders	Guava's leaves contain quercetin, a flavonoid that has an anti-diarrhea effect. Quercetin is the main active ingredient producing a spasmolytic effect. Multivitamins in some cases can produce digestive disorders; there could be synergic effects with guava.

In Cuba, 877 instances of adverse effects were reported by the National Centre for State Quality Control of Drugs from 2003 until the first semester 2007, mainly from phytomedicines, acupuncture and medicines from apitherapy medicine. Other products reported were garlic, aloe, imefasma (mixture of banana stem, flowers of *Hibiscus elatus,* and *Aloe vera*), orange and propolis /40/.

There have been 71 reports of side effects resulting from the co-administration of conventional drugs and traditional medicines; the main pharmacological groups involved are antibacterials, analgesics antihypertensives, sedatives ansiolitics, and diuretics /41/.

Females had an adverse effect incidence of 60.3% with an adult prevalence. These side effects were classified as 66% low severity, 29% moderate and 0.2% serious reactions. All of the reports were analyzed using the classification system of Karch and Lasagna /42/. These results show that in general traditional and complementary medicines were safer than conventional drugs. However, traditional medicines can also have side effects so it is important to carry out pharmacovigilance studies for this type of medicine as well.

Table 2 shows the main interactions and adverse effects found in Cuba. In Table 3, we show three examples of interactions and their proposed mechanism of action.

CONCLUSIONS

According to the data presented here it is very important to study interactions between herbs and conventional medicines, so that pharmacovigilance has now become an essential component of drug regulation. For all medicines there is a trade off between the benefits and the potential for harm. To minimize harm, the medicines are of good quality, safety and efficacy. The expectations and concerns of the patient need to be taken into account when therapeutic decisions are made.

Drug-drug interactions can affect drug systemic levels, resulting in variations in drug response of co-administered drugs. In addition, the co-administration of other drugs, concomitant ingestion of dietary supplements or citrus fruit or fruit juice could also alter systemic exposure of drugs, thus leading to adverse drug reactions or loss of efficacy. Therefore, it is important to evaluate potential drug inter-

actions prior to market approval as well as during the post-marketing period.

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