

Herbal medicines: adverse effects and drug-herb interactions

Sarah Spiteri Staines B.Pharm(Hons.), PgCert Therapeutics, PgDip Clinical Pharmacy

Pharmacist, Medicine and Poison's Information Section
Pharmacy Department, Mater Dei Hospital, Malta
Email: sarah.spiteristaines@gmail.com

Educational Aims

- To help clear the 'myth' that herbal medicines are entirely safe as they are derived from natural sources.
- To provide an overview of the different, potential types of drug-herb interactions.
- To highlight the importance of asking patients about herbal medicine use and to check for any possible interactions with their medications.

Key words

Herbal medicines, adverse effects, interactions, drug-herb interactions

With the aim of moving away from the 'synthetic' world towards a more 'organic' world, patients are increasingly seeking herbal remedies to self-treat medical conditions. Most clinicians are oblivious to their patients' use of herbal medicine. All medicinal agents have potentially unexpected effects including toxicity and interactions, and herbs are no different. Drug-herb interactions are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions. Herbal medicines do not need to be avoided, the only fundamental issue is that they should be considered as medicine and the adverse effects and potential interactions considered. Thus pharmacists and doctors should be better informed to minimise patient harm.

Definition and Description

For centuries before the beginning of scientific medicine, traditional medicine of various cultures around the world employed the use of medicinal plants as disease remedies. Products made from plants that are used to maintain or improve health have been called herbal medicines, remedies, supplements, botanicals or phytomedicines.^{1,2}

Herbal Medicine may therefore be defined as:

*Plant derived material or preparations with therapeutic health benefits, which contain either raw or processed ingredients from one or more plants(WHO 2005).*³

Introduction

With limited regulatory oversight and strong advertising, many herbal products have made their way into pharmacies and health shops and into patients' self-prescribed therapy. The internet has also become part of the marketplace. With the aim of moving away from the 'synthetic' world towards a more 'organic' world, patients are increasingly seeking herbal remedies to self-treat medical conditions, complement conventional therapies, and maintain their overall health and well-being.^{2,4}

Most patients receive their information about herbs and supplements from sources other than their healthcare provider.^{2,4} Clinicians are often oblivious to their patients' use of herbal medicines for a variety of reasons. Being natural products, patients wrongly believe they are always safe, others fear that healthcare professionals may have negative attitudes towards their use and do not report using such remedies to avoid confrontations. In addition, healthcare professionals are often not likely to ask patients about their self-medication.^{2,4}

Negative effects can result from this lack of communication, which could include adverse effects or drug-herb interactions.^{1,4} Patients may also substitute herbal remedies for more conventional therapies without informing their doctor.²

Recently, most often unaware to both the healthcare professional and the patient, several dietary and multi-vitamin supplements began to introduce herbs into their preparations. Preparations for improved joint function, improved performance, hair and eye supplements, sleep aids, weight loss and advancing age are among the preparations which are including herbs. Hence, herbal medicines may also be

consumed by those patients who did not specifically request their use.

Adverse effects and Interactions

All medicinal agents have potentially unexpected effects including toxicity, and herbs are no different.^{1,2,4-11} As with other drugs, the risk of unexpected effects may be influenced by a user's age, gender, genetics, nutrition status, and concurrent disease states and treatments.^{2,4,9} In clinical practice recognizing adverse effects of herbal medicine is not routine and their reporting is even less frequent.^{2,4-9}

It is important to be aware of any substances that have the potential to cause toxicities and to interact with prescribed medications. Most adverse reactions involve the skin, liver, GI tract but can involve the heart (e.g.ephedra). Significant hepatotoxic effects were reported with kava or echinacea when taken concurrently with other hepatotoxic drugs. The use of a drug and a herb that are both associated with potential hepatotoxic effects should be avoided.²

Even less is known about interactions than about adverse effects and much is based on speculation or on theoretical interactions rather than evidence-based and many have only been observed *in vitro* and not *in vivo* (Table 2)⁵⁻⁹ It is important to note that *in vitro* effects are not necessarily replicated *in vivo*. Findings *in vivo* often appear weaker than those *in vitro* which would suggest that a clinical study is warranted.⁹

An interaction may involve having the herb component to cause an increase/decrease in the amount of drug in the blood stream.^{5,6,9} Drug-herb interactions are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions.^{1,5,8,9}

Pharmacokinetic Interactions

Absorption

Interactions affecting absorption result in a reduction/increase of the absorption of the drug.¹⁻⁹ Changes in intestinal pH, complexing mechanisms and drugs affecting intestinal motility will affect absorption.⁵ For example, herbs such as aloe leaf, guar gum and senna, which are common ingredients in herbal weight-loss products, exert a laxative effect that may decrease intestinal transit time and reduce drug absorption. St. John's Wort induces intestinal P-glycoprotein, which may decrease the absorption of

common P-glycoprotein substrates, such as digoxin.^{5,6,8,9} Such effects may be reduced if the drug is consumed 1 hour before or 2 hours after the herb.¹

Distribution

A drug with high plasma protein binding (e.g. warfarin, carbamazepine) that has a small volume of distribution may be displaced by a herb competing for the same binding sites.^{1,5,6,8} Drug displacement from protein-bound forms, by concurrent drug administration, causes an increase in serum drug levels and which may lead to an increase in therapeutic effect.^{2,5,8}

Metabolism

Enzyme Induction

A decrease in the amount of drug could occur

by stimulating the production and activity of enzymes that degrade the drug and prepare it for elimination from the body.^{2,5,8,9} Such is the case with St. John's Wort which induces the cytochrome P450 enzymes which are responsible for the metabolism of several drugs.^{1,2,4-11} This is a common mechanism and applies to the way in which St. John's Wort may reduce the efficacy of the oral contraceptive pill or blood levels of warfarin, digoxin, protease inhibitors, theophylline, carbamazepine.^{4,5-11}

Enzyme Inhibition

The opposite may also occur, in which the herb inhibits the production of the enzyme required to break down the drug, hence increasing the drug levels.^{5,8,9} Unlike enzyme induction, which may take several days or

Table 1: Recommended Herbal Medicine References

National Center for Complementary and Alternative medicine. CAMCitationIndex.

Available at: <http://nccam.nih.gov/health/herbsataglance.htm>

Literature citations (with abstracts) of all aspects of alternative medicine. Free.

NIH Office of Dietary Supplements. IBIS Database. Available at: <http://ods.od.nih.gov/>

Literature citations (with abstracts) of dietary supplements including vitamins, minerals, and botanicals. Free.

Alternative Medicine Foundation, Inc. HerbMed. Available at: <http://www.herbmed.org/index.asp>

Online monographs of 20 popular herbal products. Literature-based reviews with references. Free. Subscription required to view entire database (233 herbs).

Natural Medicines Comprehensive Database. Available on: <http://www.nlm.nih.gov/medlineplus/druginfo/natural/607.html>

Provides online monographs of popular herbs. Free.

World Health Organisation, Geneva. 2011. Available on: <http://apps.who.int/medicinedocs/en/d/Js2200e/>

Provides online monographs of 90 popular herbs. Free.

Baxter K, Driver S, Williamson E. Stockley's herbal medicines interactions. London:Pharmaceutical Press;2009.

Literature-based review of more than 150 herbs with particular reference to their interaction profile. Online version available with subscription on *MedicinesComplete* (<http://www.medicinescomplete.com>)

Barnes J, Anderson LA, Phillipson JD. Herbal medicines: A guide for health care professionals. London: Pharmaceutical Press; 2007.

Herbal monographs. Literature-based reviews with references. Online version available with subscription on *MedicinesComplete* (<http://www.medicinescomplete.com>)

Fetrow CW, Avila JR. Professional's handbook of complementary and alternative medicines. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2004.

Herbal monographs. Literature-based reviews with references.

Table 2: Herb-Drug Interactions of particular concern

(N.B.This is not an exhaustive list. Many reactions are theoretical and have only been observed *in vitro*)^{1,4,5,6,9-15}

Drug or Drug Class	Herb(s)	Effect
Anaesthetics	Kava, Hawthorn, St John's wort, Valerian	Excessive sedation, delayed emergence from anaesthesia
Opioid –analgesics	Valerian, Ginseng, St. John's wort	Additive CNS depression Reduced analgesic effectiveness
Antidepressants	St John's wort, Ginkgo	May increase serotonin levels. May lead to serotonin syndrome with other serotonergic agents
Antidiabetic agents	Garlic, Ginseng, Milkthistle, Damiana, Eucalyptus, Fenugreek, St. John's wort	May cause hypoglycaemia
	Ephedra, Licorice	May cause hyperglycaemia
Anticonvulsants	Ginkgo, Ephedra, Evening primrose oil	May increase risk of seizures, decrease drug effect
Antihypertensives	Ephedra, Devil's Claw, Guarana (caffeine), Licorice, Ginseng	May cause hypertension
	St. John's wort	Reduced effectiveness of some anti-hypertensives
Benzodiazepines	Valerian, Kava, Hawthorn, Hops St. John's wort	Excessive sedation Reduced effectiveness
Corticosteroids	Echinacea (<8wks use), Licorice	Immunostimulant effect of herb may offset immunosuppressant effect of corticosteroids.
	Echinacea (>8wks use)	May potentiate effect of immunosuppressant.
Immunosuppressants	Echinacea, Licorice	Immunostimulant effect of herb may offset immunosuppressant effects.
	St. John's wort	May reduce immunosuppressant levels
Digoxin	Licorice, Cascara, Senna, Aloe, Cassia	May cause hypokalemia (patient more vulnerable to digoxin toxicity)
	Ginseng	May cause falsely elevated digoxin levels
	St. John's wort	Decreases digoxin levels
Diuretics	Ginseng, Licorice	Decreases diuretic effects
Warfarin/anti-platelets/ anticoagulants	Feverfew, Ginger, Ginkgo, Garlic, Saw palmetto, Guarana, Passiflora, Cat's claw, Cranberry, Evening primrose oil, Dandelion, Bilberry, Boldo	May increase anticoagulant effects of warfarin
	Ginseng, Green tea, St. John's wort, Chamomile	May decrease anticoagulant effect of warfarin

HIV medication	Garlic, St John's wort, Milkthistle, Gingko Ginseng, Echinacea - use only short-term	May decrease protease inhibitor concentrations, increase risk of antiretroviral resistance
NSAIDS	Garlic, Gingko, Feverfew	Increased risk of bleeding
Laxatives	Licorice, Senna, Cascara	Increased risk of hypokalaemia
Oral Contraceptives	Licorice	Increased risk of fluid retention, hypertension
	Ginseng	Additive estrogenic effects
Proton-pump inhibitors	Cranberry, Gingko, St John's wort	Reduced effectiveness of PPIs
Antibiotics	Dandelion, Fennel	Decreased effectiveness of Fluoroquinolones
	Cinnamon	Decreased effectiveness of Tetracyclines Increased risk of phototoxicity with tetracyclines
	St John's wort	

weeks to develop fully, enzyme inhibition can occur within 2-3 days resulting in a rapid development of toxicity.⁹ Licorice decreases the metabolism of corticosteroids, leading to adverse and toxic effects from the build-up of corticosteroids.^{1,9,11}

Evidence obtained in vitro suggests that echinacea and chamomile may inhibit the cytochrome P450, isoenzyme CYP3A4. Concurrent use with drugs like alprazolam, simvastatin, calcium-channel blockers, and protease inhibitors could potentially increase serum drug levels and adverse effects.⁶⁻¹¹

Excretion

Changes in excretion may also affect serum drug levels. Herbal diuretics are quite weak and unlikely to cause large problems.⁵ However, chronic ingestion of licorice may result in hypokalemia and water retention and accordingly may interfere with various medications including antihypertensive and antiarrhythmic agents.^{7,8}

Pharmacodynamic Interactions

Additive interactions

A herb might produce the same kind of effect as the drug and give an increase in the drug effect (without increasing the amount of the drug).^{5,8,9} Therefore herbal sedatives, anticoagulants, antihypertensives and others may possibly increase the effect of a concurrent conventional drug taken for the same purpose. For example, the hypnotic activity of benzodiazepines is increased by valerian, and the anticoagulant action of warfarin is enhanced by gingko, garlic and ginger.^{1,5,8-11}

St John's Wort together with other serotonergic drugs e.g. SSRIs may produce the additive effect of the serotonin syndrome characterised by altered mental status, autonomic dysfunction and neuromuscular abnormalities.⁹

Antagonistic interactions

A herb might produce an effect that is contrary to the effect desired for the drug, thereby reducing the drug effect.^{5,8,9} Ephedra or caffeine-containing herbs (cola nut, guarana, mate, green tea), often used in combination for the additive cardiovascular effects in many herbal weight-loss products, may antagonize the effects of antihypertensive medications.^{5,8}

Conclusion

The fact that herbal medicines also have adverse effects and may give rise to potential drug-herb interactions does not imply that their use should be discouraged. Herbal medicines are not placebo and have been found to be efficacious,⁹⁻¹¹ sometimes being a suitable alternative to conventional drugs. Most herbal drugs have good safety profiles however, the fact that they are often taken over a long period of time in various drug cocktails, may provide the opportunity for enzyme induction/inhibition to take place⁵. The only fundamental issue is that they should be considered as medicines and their adverse effects and potential interactions considered.^{2,4,5-9} Health care providers need to look closely at the risks and benefits of herbal medicines, just as they do with conventional medicine.^{2,4,5-9} In order that this may occur it is important that pharmacists and doctors should be better informed on herbal medicines.^{2,8,9-11} Ideally more importance should be given in undergraduate course and Continuing Educational Programmes addressing herbal medicines should be offered to health professionals.^{2,4,8}

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Key points

- Pharmacists/doctors must take the initiative in creating opportunities to discuss herbal medicines with patients.^{2,4}
- Healthcare professionals must be aware of the dietary/multivitamin preparations which contain herbal medicines.
- Healthcare professionals must have access to reliable reference materials^{4,8-11} (Table 1) and utilise the Medicine Information Services at Mater Dei Hospital where a team of pharmacists are available to offer help on any enquiry including herbal/complementary medicine. (Contact number – 2545 6504).
- Pharmacists/doctors must be on the alert with regards to drugs having a narrow therapeutic window or where it is necessary to keep serum levels above a suitable level (e.g.anticoagulants, antidiabetic, antiepileptic, antihypertensive, anti-infective, immunosuppressants etc.)^{5,8,9}
- Pharmacies should only stock herbals from reputable manufacturers.^{2,4,5,9-11}
- Herbal medicines should be avoided in pregnancy/lactation and used with caution in patients with reduced liver/renal function.⁹⁻¹¹
- The stated dosage and duration of dosage should be adhered to.^{4,9-11}
- Patients should be advised to be alert to possible adverse effects and interactions with lab results.^{2,4,9-11}
- Herbal medicines should be stopped at least 7 days before surgery.⁹
- Patients should be advised not to take herbal medicines and conventional medications together or at the same time.^{4,8,9}