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Herb-drug interaction: The importance of communicating with primary care physicians

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EDITORIAL

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Introduction

Herbal medicines have been perceived as natural, safe, and economically and socio-culturally acceptable remedies to many illnesses. Complementary and alternative medicine (CAM) includes herbal medicine and yoga as well as homeopathy, chiropractic care, and acupuncture. Herbal products are an important component of complementary and alternative medicine.[1] In the United States, complementary and alternative medicine is an approximately $9 billion dollar market, approximately three per cent of national ambulatory healthcare expenditures.[2] However, due to intrinsic pharmacokinetic and dynamic interactions, variability in herbal product compositions, unsupervised self-administration, and lack of adequate knowledge about the ingredients and their pharmacological properties, there is a serious risk of potentially adverse herb-drug interactions.

Worldwide prevalence of the use of CAM

A cross-sectional study comprising 463 patients suffering from chronic pain and receiving primary care at 12 US academic health centres showed widespread prevalence of CAM.[1] Users of CAM may use conventional and complementary medicines simultaneously, and this raises concerns about herb-drug interactions.[2] Physicians may be uncertain about the effects of concomitant use of herbs and allopathic medicines. A study of prescription and use of CAM among physicians and patients in a tertiary hospital in India showed that although doctors use herbal medicines more than patients (58 per cent compared to 38 per cent), they seldom enquired about herbal supplement usage among their patients.[3] The same study showed that only 15 per cent of the doctors taking herbal supplements were aware of the sources of information about those products. A national survey among university hospitals in Sweden showed a lack of adequate knowledge about herbal supplements and other CAM modalities among registered healthcare providers in surgical care.[4]

In the United States, herbal medicine and yoga became popular as CAM between 1997 and 2002.[5] However, the surge stabilised and the prevalence rates slightly declined from 18.9 per cent in 2002 to 17.9 per cent in 2007 and 2012 as evidenced by population health interview surveys conducted in those respective years.[6] A 2007 survey revealed that approximately 33 per cent of US adults who used herbal supplements disclosed it to their physicians.[7] Patients largely self-medicated without informing their doctors.[7] Figures were even worse (19 per cent) in an Indian setting.[3]

Physicians' perspective and knowledge about herbs and other CAM modalities

Physicians are largely divided on the use of herbal medicine and other CAM modalities.[8] American physicians are generally sceptical about the use of herbs and

supplements.[8] A systematic review of CAM studies has shown that both physician and patient attributes are integral for adequate physician-patient communication about the use of herbal products and other CAM modalities.[9,10]

Despite personal reservations, physicians need to be aware of patients' CAM usage in order to practice clinical medicine effectively. This has been shown to be particularly true when treating patients belonging to minority groups. One study showed the rate of non-disclosure of herbal medications was higher among racial and ethnic minority groups and among non-citizens. Impairments in language, diverse cultural factors, and economic reasons have limited the access of such subpopulations to conventional medical care.[11]

Increasing physician awareness about CAM and herbal products

We believe that steps must be taken to improve knowledge, attitudes, and perceptions about herbal medications amongst primary care and general physicians, as well as to improve physician-patient communication. Ways to integrate herbal and alternative medicine into mainstream conventional medicine include more pharmacokinetic research, conducting studies involving pharmacogenomics (the study of how genes can affect an individual's response to drugs) and adverse drug events, offering continuing medical education (CME) credits for alternative medicine courses, and encouraging active collaboration between conventional medical providers and CAM providers.[12] Ways to strengthen effective physician-patient communication should include emphasis on communication and interpersonal skills, cultural sensitivity issues, cost effectiveness, understanding the faith and practice of the community, and most importantly, awareness regarding different CAM therapies.

Clinical implications of herb-drug interactions

Herbs can increase or decrease a prescription drug's expected activity, leading to either unwanted adverse effects or therapeutic failure. Active ingredients in the herbs can alter remarkably the pharmacokinetic and pharmacodynamic properties of a drug. For example, Co-enzyme Q10, a widely used food supplement, interferes with the efflux transporter P-glycoprotein and thus alters the pharmacokinetics of many drugs.[13] In contrast to drug-drug interactions, it is difficult to access information about herb-drug interactions. With the exception of some review articles, reliable resources for such information are limited. Table 1 outlines some common herb-drug interactions.

The pharmacological effect of a drug depends on its concentration at its site of action, which in turn depends on its rate of elimination. In many drugs, hepatic microsomal enzymes govern this. Inducers of the CYP450 hepatic microsomal system can result in rapid elimination and reduced bioavailability of certain drugs and may result in therapeutic failure, whereas opposite effects may be encountered when the same enzyme system is inhibited. Drug elimination is reduced and plasma half-life is increased manifold, which can lead to unwanted adverse effects.

Common herb-drug Interactions

Many herbs have the potential to induce the CYP450 enzyme system. Perhaps the most notable is St. John's Wort (*Hypericum perforatum*), which reduces the plasma concentration of many drugs such as amitriptyline, digoxin, theophylline, non-steroidal anti-inflammatories (NSAIDs), and oral contraceptive pills.[13] St. John's Wort also increases the activity and expression of multidrug transporter P-glycoprotein efflux pumps in the duodenum. This mechanism has been implicated in its interactions with indinavir, digoxin, and cyclosporin. It also increases the metabolism of protease inhibitor indinavir, resulting in therapeutic failure. It has also been implicated for reducing cyclosporine bioavailability, an immunosuppressive agent given in transplant recipient patients.[14,15]

In conjunction with the use of medicinal herbs at the same time as warfarin, serious adverse effects have been encountered with warfarin due to herb-based inhibition of its metabolising enzymes. These include spontaneous postoperative bleeding, haematomas, haematemesis, melena, subarachnoid haemorrhage, subdural haematomas, and thrombosis. The herbs that can cause such adverse reactions include: Panax ginseng, Hypericum perforatum (St John's Wort), Gingko biloba, Serenoa repens, Angelica sinensis, Vaccinium species, Allium sativum (garlic), Zingiber officinale (ginger), Tanacetum parthenium, Lucium barbarum, Matricaria chamomilla, Boswellia serrate, and Camellia sinensis (tea).[15] Zingiber officinale (ginger) is a common herbal medication that is used in motion sickness and inflammation. Ginkgo biloba is another common herbal remedy that is reputed to increase mental alertness. St John's Wort is an herbal remedy for treating depression. Vitamin K, a naturally occurring vitamin, is principally found in green leafy vegetables. It is suggested that Vitamin K intake from the diet should be restricted to 65–80 micrograms in patients who receive warfarin.[15] Dietetic advice is recommended. Accordingly, physicians need to be aware of patients' dietary habits, in addition to any unsupervised intake of

herbal medications in order to prevent hazardous side effects.

The commonly used dietary supplement liquorice contains glycyrrhizin and glycyrrhetinic acid.[16] These are potent inhibitors of 11-βhydroxy steroid dehydrogenase, causing raised cortisol and increased mineralocorticoid activity, leading to hypertension and suppression of the renin-angiotensin aldosterone system. Liquorice also interacts with various medicines such as some antihypertensives and some antiarrhythmics. Furanocoumarins found in grapefruit juice are potent inhibitors of the CYP enzyme system; bergamottin is the most potent of all. Furanocoumarins are found in many Chinese herbs. Flavonoids found in some herbal remedies also can cause significant inhibition of the CYP3A4 system. Similarly, people taking mono amine oxidase inhibitors (MAOIs) as prescription medications should avoid consuming Scotch broom (*Cytisus scoparius*) (which contains tyramine), as the combination may trigger a hypertensive crisis. Ginger, used by traditional Western and Chinese medicine to treat nausea, inactivates pro-emetic substances in the stomach. The same mechanism can hinder the absorption of certain drugs and neutralise their effect. Ginger can hinder the absorption of drugs by deactivating them in the stomach and therefore reducing their absorption.

Herbs of the genus Rehmannia have been shown to antagonise suppressant effect of steroids on the hypothalamic-pituitary-adrenal axis. In such cases, the physician needs to tailor the patients' dose of steroids. Lower than usual therapeutic dose needs to be administered, otherwise adverse effects relating to increased steroid levels in the blood will increase. [17]

Conclusion

As herbal supplement use becomes increasingly popular, issues regarding the safety of co-administration of these products together with conventional medicines need to be highlighted. Potential herb-drug interactions can be avoided by prescribing them in such a way that they do not result in any unwanted pharmacokinetic interaction, or by reducing the dose in case both the herb and the pharmaceutical drug have the same therapeutic action. (e.g., sedatives and hypoglycemic agents). Those who are elderly, debilitated, or receiving polypharmacy are more at risk for an herb-drug interaction and particular attention is required in these cases. For patients using CAM, it is essential for the physician to know more about the mechanism of action of drugs and herbs. An effective educational intervention could bridge this gap between acceptance and knowledge about CAM. Awareness programmes about the widespread usage of CAM should be organised for healthcare practitioners as well as medical students. Integration of herbal medicines into the curriculum of modern medicine programmes and continuing medical education, an interdisciplinary approach between the practitioners of herbal medicine and conventional medicine, and the availability of reputable pharmacopeias for reference are some of the ways to improve the situation.

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PEER REVIEW
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CONFLICTS OF INTEREST
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Table 1: Common herbal supplements, their usage (in brackets) and potential interactions with prescription drugs[18–25]

Herb	Drug	Mechanism of interaction	Effect
St. John's Wort *Hypericum perforatum* (depression)	Digoxin	Induction of P-glycoprotein by St. John's Wort	Reduction in serum digoxin level by 18–25 per cent
St. John's Wort *Hypericum perforatum* (depression)	Indinavir	Induction of cytochrome P450 (Cyp450)	A 57 per cent reduction of Indinavir area-under-the-curve (AUC)
St. John's Wort *Hypericum perforatum* (depression)	Clopidogrel (Plavix)	Induction of cytochrome P450 (Cyp450)	Decline in platelet aggregation
St. John's Wort *Hypericum perforatum* (depression)	Tacrolimus	Induction of cytochrome P450 (Cyp450)	Lower blood levels of the drug
Ginkgo biloba	Acetaminophen	Antiplatelet activity	Increased bleeding time up to 15 min
Ginkgo biloba	Sodium valproate	Unknown	Reduced seizure threshold
Co-enzyme Q	Warfarin	Procoagulant activity	INR reduced from 2–3 to 1.31
Ginger (*Zingiber officinale*)	NSAIDS	Unknown	No symptomatic relief from pain
Ginseng (*Panax ginseng*)	Warfarin	Unknown	INR declined to 1.5
Kava (*Piper methisticum*)	Promethazine biperiden	Dopamine antagonism	Involuntary neck extension
Grapefruit juice	Fluoxetine trazodone	Inhibition of CYP450	Serotonin syndrome
Grapefruit juice	Simvastatin	Inhibition of CYP450	Rhabdomyolysis, muscle weakness
Grapefruit juice	Quinine	Flavonoid naringen increases Quinine bioavailability	Torsades de pointes
Grapefruit juice	Warfarin	Unknown	GIT, pericardial haemorrhage