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Herbal drugs in milieu of modern drugs

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Medicinal herbs are moving from fringe to mainstream use with a greater number of people seeking remedies and health approaches free from side effects caused by synthetic chemicals. Most people believe that herbs are harmless plants, but when these are taken concurrently with drugs, interactions are possible. In this review article, we have discussed several popular herbs, and attempted to provide a comprehensive review that summarizes drug-herb interactions. Mustering systematic information about drug-herb interactions will be a Herculean task. The hurdles in evaluating herbal drugs include lack of standardization, insufficient quality control, overall under-reporting, etc. The challenges posed in evaluating and improving the safety of herbal drugs are the need for standardization and quality control, official compendia, dissemination of information, additional research, pharmacovigilance and regulations. With concentric efforts to surmount these challenges, the wealth of traditional knowledge can be put to judicious use in the form of herbal remedies and that it finds a rightful place in the health care system.

Key words: Current status, standardization, quality control, regulations, herb-drug interactions

INTRODUCTION

Three decades ago, only few had any appreciation of the number of remedies that had their origin from herbal medicine, and most had vague knowledge of herbal medicine, traditional medicine or other forms of complementary and alternative medical practices (Lipp, 1996). For a variety of reasons, more individuals nowadays prefer to take personal control over their health with the use of herbal medicines, not only to prevent diseases but also to treat them. This is particularly true for a wide variety of illnesses readily treated at home (common cold, etc.) (Kincheloe, 1997). Herbal products are also commonly used by patients with certain chronic medical conditions, including breast cancer (12%) (Burststein, 1999), liver disease (21%) (Strader, 2002), human immunodeficiency virus (22%) (Kassler, 1991), asthma (24%) (Blanc, 2001) and rheumatological disorders (26%) (Rao, 1999). WHO estimates that about three-quarters of the world's population currently use herbs and other forms of traditional medicines to treat their diseases. 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.

The acceptance and recognition of herbal medicine has been in part due to the acknowledgement of the value of traditional and indigenous pharmacopoeias, the incorporation of some medicines derived from these sources into pharmaceuticals (DeSmet *et al.*, 1992a; Winslow and Kroll, 1998), the need to make health

care affordable for all and the perception that pharmaceutical drugs are increasingly overprescribed, expensive and even dangerous. Another important perception fomenting this interest is that natural remedies are somehow safer and more efficacious than remedies that are pharmaceutically derived (Bateman *et al.*, 1998; Murphy, 1999).

HERBAL MEDICINE

The increasing awareness of herbal medicines is acknowledged by 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 are 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 preparations for therapy.

Herbal Medicine - Current Status

The art of herbal medicine is extremely ancient, probably predates the modern *Homo sapiens* (Bensky and Gamble, 1993). In ancient cultures, people methodically and scientifically collected information on herbs and developed well-defined herbal pharmacopoeias. The earliest recorded evidence of such efforts in Indian, Chinese, Egyptian, Greek, Roman and Syrian texts dates back to about 5000 years. The classical Indian texts were *Charak Samhita* and *Sushruta Samhita*.

Irrespective of the decline in use of herbal medicines, the importance of botanicals in the evolution of medicine

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remains unchallenged. Many drugs are developed with phytochemicals or taking phytochemicals as lead molecules. Some valuable mainline drugs include digitalis, cinchona, taxol, ergotamine, morphine, cocaine, reserpine, among numerous others. Despite the importance of plant-led discoveries in the evolution of medicine, some regulatory bodies such as the U.S. Food and Drug Administration (FDA) consider herbal remedies to be insignificant or potentially dangerous. Indeed, today in the United States, herbal products can be marketed only as food supplements under Dietary Supplement Health and Education Act of 1994 (DSHEA), and a manufacturer or distributor cannot make a specific claim on the label regarding the ailments for which the product might be used without seeking approval from FDA.

With or without interference from the regulatory authorities, the use of herbal medicines is on the surge and the market is increasing day by day (Kamboj, 2000). The global market for herbal medicines currently stands at over \$60 billion annually. Sales are projected to increase at an average annual growth rate of 6.4%. In India, the herbal drug market is about \$1 billion.

Drug Interaction

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. Consumers of herbal medicines tend to be affluent, middle aged and chronically ill (Eisenberg, 1998). They are thus likely to combine herbal medicines with prescriptive drugs. Hence, the risk of drug interactions increases, because more the number of products consumed more the risk of interactions. The fact is that many herbal remedies have the potential to cause adverse drug interactions when used in combination with various prescription and over-the-counter pharmaceuticals.

The mechanisms of drug interaction fall into two general categories: pharmacokinetics (absorption, distribution, metabolism and excretion of a drug) and pharmacodynamic interactions (the combined pharmacological effects of drugs). The mechanism of action of many herbs has not been understood. Therefore, the exact mechanism of drug-herb interaction is also unknown. 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 are apt to bind to other drugs, particularly when consumed in whole or in powdered form. For example, psyllium (an herb rich 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 (e.g. digoxin, warfarin). Herbs such as meadowsweet

and black willow, which contain pain-reducing salicylates, may displace highly protein-bound drugs such as warfarin and carbamazepine, thus amplifying adverse effects of the drugs. Licorice (as an herb, not a sweetener) decreases the metabolism of corticosteroids, leading to adverse and toxic effects from the build-up of corticosteroids (Chen, 1991). Recently, researchers have 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, including digoxin and theophylline, protease inhibitors and cyclosporine (Lantz, 1999). An example of 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 many other herbs. Dangerously low blood pressure levels may result from the combination of an herbal remedy that lowers blood pressure together with a prescription medicine that has the same effect. In particular, many herbs should be avoided during pregnancy. The list of herbal medicines that have a potential for such interactions seems endless (Table 1).

DIFFICULTIES IN EVALUATING SAFETY

Lack of Standardization

Consistency in composition and biologic activity is essential for safe and effective use of therapeutic agents. However, botanical preparations rarely meet these standards because of problems in identifying plants, genetic variability, variable growing conditions, differences in harvesting procedures, storing and processing, nature of formulation and, above all, lack of information about active pharmacologic principles (Marcus, 2002).

Botanical identity can be difficult to establish since two different collectors may call two different drugs by the same name. For example, *Sarothami scoparii flos* can be of two different species as *Sarothammus scoparius* and *Spartium junceum*. Such kind of misunderstanding may lead to serious adverse conditions. For example, the replacement of *Stephania tetrandra* (fangji) with the root of *Aristolochia fangchi* (guangfangji) in a slimming treatment that included conventional medicines had resulted in numerous cases of progressive renal interstitial fibrosis, complicated in some persons by urothelial carcinoma (Nortier, 2000). Similar problems may arise when a Chinese herbal ingredient 'mutong' is taken from *A. manshuriensis* (guanmutong) instead of akebia or clematis (Lord, 1999, 2001).

Product identification is the next obstacle. Many commercially available products contain multiple ingredients. For instance, Sinupret (Bionorica), the best-selling herbal medicinal product in Germany, contains five

Table 1: Different types of interaction between herbs and pharmaceutical drugs

| Herb | Pharmaceutical drug | Comments | References |
|---|---|--|--|
| Aloe gel and juice (<i>Aloe vera</i>) | Insulin or oral hypoglycaemic | Additive effects | Aslam, 1979; Yongchaiyuda <i>et al.</i> , 1996 |
| Bitter melon (<i>Momardica Charantia</i>) | Insulin | Additive effects | Baskaran <i>et al.</i> , 1990; Escop, 1997 |
| Betel nut (<i>Areca catechu</i>) | Flupenthixol, procyclidine, fluphenazine, prednisone and salbutamol | Rigidity, bradykinesia, jaw tremor, stiffness, akithesia. Inadequate control of asthma. Betal contains arecoline, a cholinergic alkaloid. Arecoline challenge causes dose-related bronchoconstriction in asthma patients | Deahl, 1989; Taylor, 1992 |
| Chilli (<i>Capsicum spp</i>) | Theophylline | Cough, increased absorption and bioavailability | Hakas, 1990 |
| Danshen (<i>Salvia iltiorrhiza</i>) | Warfarin | Increased INR in rats; danshen decreases elimination of warfarin | Chan, 1995; Cheng, 1999 |
| Devil's claw (<i>Harpagophytum procumbens</i>) | Warfarin | Purpura | Shaw, 1997 |
| Dong quai (<i>Angelica sinensis</i>) | Warfarin | Dong quai contains coumarins; increased INR and widespread bruising | Page, 1999 |
| Siberian ginseng (<i>Eleutherococcus senticosus</i>) | Digoxin | Raised digoxin concentrations | McRae, 1996 |
| Ephedra (<i>Ephedra sinica</i>) | Guanethidine | Enhances sympathomimetic effect | Blumenthal, 2000 |
| Garlic (<i>Allium sativum</i>) | Warfarin | Increased INR post-operative bleeding and spontaneous spinal epidural haematoma | German, 1995 |
| Ginkgo (<i>Ginkgo biloba</i>) | Aspirin, paracetamol, ergotamine, caffeine, warfarin, thiazide diuretic | Spontaneous hypHEMA; potent inhibitors of PAF; subarachnoid haemorrhage and subdural haematoma; intracerebral haemorrhage; hypertension | Chung, 1987; Rowin, 1996; Rosenblatt, 1997; Vale, 1998 |
| Ginseng (<i>Panax spp</i>) | Warfarin | Decreased INR in rats; concomitantly administered ginseng had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin | Zhu, 1999 |
| Danshen (<i>Salbia militorrhiza</i>) | Warfarin | Potentiates warfarin activity | Tam, 1995 |
| Valerian (<i>Valeriana officinalis</i>) | Antidepressants, antihista minics, antispasmodics | Drowsiness; potentiates effects of antidepressants, antihistaminics, antispasmodics | Garges, 1998; Giedke, 2000 |
| Guar gum (<i>Cyamopsis tetragonolobus</i>) | Metformin, phenoxymethyl-penicillin, glibenclamide | Slows absorption of digoxin, paracetamol, glibenclamide and bumetanide; decreases absorption of metformin, phenoxymethylpenicillin and some formulations of glibenclamide; prolongs gastric retention | DeSmet, 1996 |
| Karela or bitter melon (<i>Momordica charantia</i>) | Chlorpropamide | Karela decreases glucose concentrations in blood | Aslam, 1979; Leatherdale, 1981 |
| Liquorice (<i>Glycyrrhiza glabra</i>) | Prednisolone, hydrocorti sone, oral contraceptives | Decreases plasma clearance orally; increases AUC, hypertension, oedema, hypokalaemia; oral contraceptive use may increase sensitivity to glycyrrhizin acid; women are reportedly more sensitive than men to adverse effects of liquorice | Chen, 1991; Bernardi, 1994 |
| Psyllium (<i>Plantago ovata</i>) | Lithium | Decreased lithium concentrations | Perlman, 1990 |
| St John's wort (<i>Hypericum perforatum</i>) | Paroxetine, trazodone, sertraline, nefazodone, theophylline, digoxin, cyclosporin, oral contraceptive | Lethargy/incoherence, mild serotonin syndrome, decreased theophylline concentrations, decreased AUC, decreased concentrations in serum, breakthrough bleeding | Demott, 1998; Gordon, 1998; Bon, 1999; Lantz 1999 |
| Shankhapushpi (Ayurvedic mixed-herb syrup) | Phenytoin | Decreased phenytoin concentrations, multiple coadministered doses (but not single dose), decreased seizure; single dose decreases the antiepileptic effect of phenytoin | Dandekar, 1992 |
| Tamarind (<i>Tamarindus indica</i>) | Aspirin | Increased bioavailability of aspirin | Mustapha, 1996 |
| Valerian (<i>Valeriana officinalis</i>) | Alcohol | A mixture of valepotriates reduces adverse effects of alcohol | Bos, 1997 |
| Yohimbine (<i>Pausinystalia yohimbe</i>) | Tricyclic antidepressants | Hypertension even at low dose | Lacombez, 1989 |

different medicinal plants. Asian herbal mixtures typically contain about twice that amount. In such cases, it is often impossible to know which ingredient caused the reported health problem.

Brand names suffer from confusion. One herbal extract can be an ingredient in dozens of different brands, and frequently identical brand names contain different mixtures of plants. Labeling of commercial products is often less than sufficient. Making associations between one herbal ingredient and a reported adverse effect can, therefore, be difficult and sometimes impossible.

Accidental adulterations in herbal remedies are particularly disconcerting since they occur so unexpectedly. Usually they remain undetected unless they can be linked to an outbreak or epidemic. An example in this respect is veno-occlusive disease due to over a hundred pyrrolizidine alkaloids found within the species of Asteraceae, Boraginaceae and Fabaceae, which can be life-threatening or fatal (Drew and Myers, 1997).

Insufficient Quality Control

In most countries, herbal medicines are not regulated as medicines but marketed as dietary supplements; hence quality control of medicines can be easily surpassed. The quality of some products has repeatedly been shown to be suboptimal (DeSmet, 2002). Some of the most extreme cases involve Asian herbal mixtures that can be contaminated, for example, with botanicals, micro-organisms, microbial toxins, heavy metals, pesticides or adulterated with powerful prescription drugs. The drugs reported were ephedrine, chlorpheniramine, ethyltestosterone, phenacetin, glyburide, sildenafil, colchicine, adrenal steroids, alprazolam, phenylbutazone and fenfluramine, and metals were lead, mercury and arsenic (Ernst, 2002; Ko, 1998; Au, 1998; Ernst, 2002). In 1991, WHO developed guidelines for the assessment of herbal medicine. The salient features of WHO guidelines were: (i) *quality assessment*: crude plant material, lant preparation, finished product; (ii) *stability*: shelf life; (iii) *safety assessment*: documentation of safety based on experience or/and toxicology studies; (iv) *assessment of efficacy*: documented evidence of traditional use or/and activity determination (animals, human).

Lack of Systematic Data

Herbal medicines are usually not patentable. Therefore, keen commercial impetus for systematic research rarely exists. Consequently, there is lack of hard data on herbal safety. Much of the available evidence is built on non-clinical investigations and is incomplete, and thus data is inconclusive in nature (Ernst, 2004). Depending on the circumstances, both under-reporting (Barnes, 1998) and over-reporting (Schulze, 2003) of herbal adverse effects have

been suspected, and the unduly strong influence of the press in this area is a well-recognized aggravating factor. Users of herbal medicine often miss to inform their doctors, and conventional healthcare professionals sometimes lack in knowledge about herbal medicine to advise their patients responsibly. As a consequence, the evidence regarding the nature and incidence of adverse effects caused by herbal medicines is woefully incomplete.

It is more difficult, however, to recognize adverse effects that develop over time, e.g. hypokalemia from anthranoid laxatives. Embryotoxic, fetotoxic and carcinogenic effects of herbal remedies are also likely to remain unrecognized in traditional settings. Although aristolochia plants have been used for centuries, their capacity to induce urothelial carcinoma by DNA-adduct formation has only recently become clear (Blumenthal, 1998). The traditional experience is not always a reliable tool for the detection of rare reactions; it has limited value in predicting risks associated with non-traditional preparations or with use under non-traditional circumstances (e.g. in combination with conventional drugs).

CHALLENGES IN IMPROVING SAFETY OF HERBAL REMEDY

Need of Standardization and Quality Control of Herbal Drugs

Consistency in the quality of herbal drugs can be maintained by adopting the Good Agricultural Practices and Good Field Collection Practices for the cultivation and collection of herbal drugs. Standard practices for preservation and presentation have to be developed and practiced similarly. For quality control and quality assurance of herbal drugs, standardization techniques with respect to authentication, purity profile and assay have to be developed and put into practice. The use of chromatographic techniques and marker compounds to standardize herbal preparations promotes consistency across batches. This, but, does not ensure consistent pharmacologic activity or stability. Moreover, analyses of purportedly standardized herbal preparations reveal that botanical products often do not actually contain the amount of a compound stated on the label (Marcus, 2002).

Need for Official Compendia

Several pharmacopoeias have provided parameters to maintain quality and standardize procedures in identification/authentication of herbal inputs and their products. Most countries have evolved their own pharmacopoeial standards; however, it is apparent that no country has a complete list of plants included in it, and there is a lot desired to format different pharmacopoeias as per recommendations of WHO. The European Pharmacopoeia

2002 has 174 monographs on herbal drugs and preparations. British Herbal Pharmacopoeia has 233 monographs; British Herbal Compendium has 84 monographs; United States Pharmacopoeia (USP) and the National Formulary has 28 official monographs of the most commonly used plants in the country. Countries with strong background of traditional medicine like China and India are leading. Chinese Pharmacopoeia 2000 has 992 monographs, and Ayurvedic Pharmacopoeia of India (API) has about 1000 single drugs and 8000 compound formulations of recognized merit used in India. The USP is also compiling standard monographs for herbal dietary supplements and dispensatory information (DI). They have already published 11 monographs and an additional 12 are under preparation.

As a complement to these efforts, a number of organizations are preparing monographs to delineate details of herbs that are popularly used as phytomedicines and medicinal plant preparations so that their recognition as official medicines may culminate. The well-recognized monographs are from German Commission E (380 monographs) and European Scientific Cooperative On Phytotherapy (ESCOP) (60 monographs). In order to set standards in documenting the quality of herbal products and outlining the therapeutic parameters for safe and effective use, the publication of WHO Monographs on Selected Medicinal Plants is ongoing with Volume 1 (1999) of 28 monographs on 31 plant species, Volume 2 (2000) of an additional 30 monographs and Volume 3 of an additional 31 plants. Moreover, the herb trade, in recognizing its responsibility to provide appropriate guidelines, has recently published through the American Herbal Products Association (AHPA) *The Botanical Safety Handbook*, 2nd edition (1998). The most ambitious attempt in this respect is that of the American Herbal Pharmacopoeia and Therapeutic Compendium, which plans to publish at least 2000 monographs of this nature.

Need of Dissemination of Information

Dissemination of information is positively important in helping the patient or consumer make educated choice; this can be expedited by making use of internet sources like the National Center for Complementary and Alternative Medicine (www.nccam.nih.gov), American Botanical Council (www.herbalgram.org), US Food and Drug Administration (www.fda.gov), the USP (www.usp.org) and International Bibliographic Information on Dietary Supplements (IBIDS) (<http://odp.od.nih.gov/ods>). Currently, IBIDS contains 400,000 citations and abstracts of published international, scientific literature on dietary supplements, including vitamins, minerals and botanicals and is updated quarterly.

Dissemination of information to the leity should be complemented by sensitizing allopathic practitioners to

the aspect of herbal products. It is known that allopathic practitioners have little training in understanding various forms of complementary and alternative medical practices even if it has impact on the health of their patients who are often also under prescriptive medication. A sensitized practitioner will be eager to acquire information from patients about concurrent use of herbal products and alternative medicines without being judgmental.

To increase sensitivity and awareness in future practitioners, a number of US medical schools are developing courses in Complementary and Alternative Medicine, including some exposure to herbal medicinal practices. The practice of sagacious use of herbal remedies should be inculcated among the users abiding to rational use of drugs and herbs.

Need of Additional Research and Surveillance of Adverse Effects

The pressing need for additional research related to traditional herbal remedies is directed toward the identification of active principles. Without the knowledge of active principles, it is difficult to standardize a product and its dose. For example, Valerian is the oldest known sleep aid; yet after 2000 years of use, we still do not know its active principles. There is urgent need to establish suitable procedures for identifying, analyzing and determining the concentration of active components in herbs. Another area of research need is of clinical trials to establish efficacy, safety and other parameters of herbal medicines in scientific and systematic manner.

Adverse effects from herbal remedies are not rare, but their frequency and severity are unknown because, other than spontaneous reporting of events and cases, there is no mechanism for collecting and assessing them. DeSmet (1995b) proposed that post-marketing surveillances (pharmacovigilance) of herbal remedies be conducted to 'detect serious adverse reactions, quantify their incidence and identify contributive and modifying factors'. Obviously, the success of such endeavors depends on those willing to voluntarily and spontaneously report such events to appropriate health care officials, pharmacologists (www.faseb.org:aspet:HandMIG3.htmctop), regulatory bodies (FDA 'MEDWATCH', www.vmcfscan.fda.gov:_dms:aems.html) and responsible parties in the herb trade industry, like the American Botanical Council (www.herbs.org), who are collating such data for public dissemination.

The Need for Regulations

1. Some herbs like the St John's wart are classified as both phytomedicines and food supplements. However, ironically, the pharmacological activity will be the same. Hence, the line of demarcation should be made clear by regulatory authorities.

2. The regulatory requirements applicable to conventional drug manufacturing should be made mandatory to herbal product manufacturing. Good manufacturing practices would help toward preventing adulteration and improving the standardization of marketed botanical products.
3. The manufacturers of herbal products should obtain pre-marketing approval from regulatory authorities demonstrating that their products present no substantial or unreasonable risk of injury under conditions of recommended use, as suggested on the label.
4. The labels of herbal products should contain a list of constituents, unambiguously identifying herbs by their botanical and common names. Information about possible adverse effects, including the risk of potential herb-drug interactions, should be included.
5. Measures are needed to ensure that non-medical practitioners who prescribe herbal medicines should receive adequate training and continuous education to reach and maintain a high standard of practice. The United Kingdom Department of Health is already making progress in this domain, having proposed statutory self-regulation of herbal practitioners.
6. The manufacturers of herbal products should compulsorily report all adverse effects promptly to the regulatory authorities analogous to post-marketing surveillance required for all prescription drugs and some over-the-counter drugs, and expert panels should review the safety of all.

CONCLUSION

The practice of herbal remedies is as old as civilization. However, it should be remembered that argument about the use of herbal remedies by ancestors since time immemorial cannot be a substitute for compiled data on their efficacy or safety. The time has come to apply scientific approach to this practice as the popularity of herbal remedies is escalating. Studies on herbal remedies with respect to their efficacy, safety profile, adverse interactions, standardization, etc. should be conducted with utmost priority not only by the manufacturers but also by the fraternity of pharmacy and medicine. Fundings should be made available for such endeavors. Patients as well as conventional practitioners should be made aware of the adverse effects of herbal remedies and their potential to cause interactions on concomitant use with conventional medicines. The government should take initiatives with respect to laying down regulations for safe use of herbal remedies and implementing them. With these concentric efforts, the wealth of traditional knowledge can be put to judicious use in the form of herbal remedies and that it finds a rightful place in health care system.

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