Herbal Medicines: Are they safe?

Milind Parle* and Nitin Bansal

1Pharmacology Division, Department of Pharmaceutical Sciences,
Guru Jambheshwar University, Post Box No. 38, Hisar-125 001, Haryana, India
2Lord Shiva College of Pharmacy, Post Box No. 63, Sirsa-125 055, Haryana, India
*Correspondent author, E-mail: mparle@rediffmail.com

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Abstract

The herbal drug industry is growing at an astounding rate all over the world. Herbal remedies are now available not only in drug stores, but also, in food stores and supermarkets. Therefore, the efficacy and safety of herbal drugs is very crucial. One of the most serious hazards associated with herbal medicines is that consumers mistakenly assume that since herbs are obtained from nature, they must be safe. However, herbal medicines need to be used with utmost caution. Strychnine, curare and morphine are a few examples of poisonous alkaloids obtained from plant source. Ginkgo biloba Linn. has been shown to be beneficial in managing Alzheimer’s disease, but is recently reported to precipitate epileptic seizures. No doubt, many herbs are found to be miraculous cures for several diseases such as vincristine for cancer treatment and codeine as an anti-tussive agent. The authors are of the view that before marketing, herbal remedies must undergo animal studies and clinical trials so as to establish their therapeutic value. This has become important, since Dietary Supplement Health and Education Act 1994 have included herbs along with vitamins, as food supplements. Thus, FDA has almost lost its control over herbal drugs. There is a need to ponder over some basic issues such as uniform nomenclature, authentication and standardization of plants and plant parts, acceptable impurities, contaminants, pharmacokinetic profile and shelf life before advocating herbal remedies.

Keywords: Herbs, Cardiotoxic, Contaminants, Hepatotoxic.

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Introduction

The use of plants for treating various diseases predates human history and forms the origin of much of the modern medicine. Long before the advent of modern medicine, herbs were the mainstream remedies for nearly all ailments. People commonly diagnosed their own illnesses, prepared and prescribed their own herbal medicines, or bought them from the local apothecaries (Tyler, 2000). Herbal medicines are being used increasingly as dietary supplements to fight or prevent common maladies like cancer, heart attacks and depression (Eisenberg et al., 1998). When added to foods as supplements, herbs have also been termed as nutraceuticals. Herbal remedies are unpurified plant extracts containing several constituents, which often work together synergistically. According to WHO, herbal medicine is defined as plant derived material or preparation, which contains raw or processed ingredients from one or more plants, with therapeutic values. Use of plant products, as medicine is inherent in Ayurveda, the ancient Indian system of health care (Dev, 1999). Several Ayurvedic preparations employ a combination of several species of plants for prevention or cure of diseases. In China, modern medicine utilizes the experience of ancient practice of herbal medicines and has worked out helpful drug regulations (Lee, 2000).

Based on ancient and experiential evidence, these culturally accepted herbal practices and beliefs are becoming quite common. Sales of herbal medicines are booming as a consequence (Brevort, 1998). According to WHO, approximately 80% of the world’s population prefer herbal drugs for their routine health care. In USA, the sales of herbal medicines are approaching $ 4 billions a year.

The reasons people use herbal medicines are diverse. However, there are a number of theories explaining the relatively recent upswing in the use of herbal medicines. The consumers’ attitudes toward the relationship between health and diet have been improving. The avoidance behaviours have grown, discouraging foods that contain preservatives and other carcinogenic materials. This concern quickly moved to ingredients such as salt, sugar and cholesterol (Wood, 1997). The increased longevity of humans has resulted in an increased interest in the “quality of life.” A large segment of population demand a multipurpose herbal medicine, which would relieve their arthritis, improve cardiovascular health and enhance mental...
Advertisements in the mass media projected herbs into the limelight. Advertisements in the mass media including television programs have increased consumer awareness and given the herbal products undue respectability and credibility (Brevort, 1998). These advertisements attract the people of all ages. Children use herbs for their nutritional values, young persons for their euphoric effects, older persons for their anti-ageing effects and women for slimming and beautifying effects.

Patient’s utilization of herbs for self-medication has a number of other reasons. Many patients are uncomfortable about discussing their medical problems and fear lack of confidentiality in handling their health information. Often, patients with non-specific symptoms or general malaise may fear possible misdiagnosis and wrong treatment. The lack of time to see a physician is commonly indicated as a reason particularly where prior visit did not result in a positive experience (Studdert et al., 1998). The patient’s freedom to “choose” a practitioner, encourage people to utilize alternative treatments and herbal medicines. Many patients select herbal medicines because of a deductive approach based on anecdotal information, that is, “it worked for my friend or relative”. Additionally, people are increasingly disposed to accepting therapeutic value of a treatment based on faith or intuition rather than scientific reasoning (Astin, 1998; Zeil, 1999). Herbal medicine approach is particularly alluring when it emphasizes the body’s natural capacity for self-repair, given appropriate conditions. Research has found that users of the herbal medicines are frequently those who strive to keep control of their lives in their own hands and need to trust effectiveness of the treatment (Astin, 1998). People also tend to believe that natural products are inherently better than synthetic drugs. The natural drugs somehow contain the “vital force” that is going to improve their health. In addition, the herbal preparations are far less expensive than prescription drugs. Herbal medicine use presents both promise and risks. The promise is of alternative and effective treatment for chronic disorders. The risk is borne out of the great-unknown effects of herbs on the human body. People who use herbal medicines for self-diagnosed ailments run potential health risks. The risks involve people of all ages (Cupp, 1999). Now, we would like to highlight some issues on which regulatory guidelines need to be laid down.

**Regulatory control**

A manufacturer must gain approval of FDA before marketing a substance as a medicine. Traditional herbal medicines cannot be patented because of stringent and inadequate patent laws and costly approval processes. Since, Food and Drug Administration (FDA) do not regulate herbal products, they cannot be labeled as useful therapeutic remedies (Glisson et al., 1999). Most herbal products are considered as dietary supplements and are not required to meet the standards specified in Federal, Food, Drugs and Cosmetics Act. For example, Ginseng was clearly characterized as a drug till recently and could be labeled and prescribed to patients as such. Today, FDA calls, Ginseng, legally a food for beverage use. Now, it is common to find Ginseng recommended for many different medical conditions. With regard to using herbs as food additives, the FDA has maintained a list of substances “Generally recognized as safe” (the GRAS list). The list contains about 250 herbs, primarily limiting their use in beverages and as food additives. The list, of course, contains no reference to herbs as drugs. In 1990, the Nutrition Labeling and Education Act required consistent, scientifically based labeling of all processed foods. Herbal medicines were still left in limbo. Finally, in 1994, Dietary Supplement and Health Education Act (DSHEA) included herbal remedies in the definition of dietary supplements. According to DSHEA, the manufacturer is responsible for controlling quality, but if a concern about safety arises, the burden of proof lies not with the manufacturer but with the FDA, which has to prove that the product is unsafe or ineffective (Ang-Lee et al, 2001). Due to lack of proper regulations and guidelines, these substances enter the market legally without ethical human trials. Herbal medicines often shield themselves behind the terms such as “natural”, “food supplement”, “herbal” and “healthy”. The consumer then becomes a guinea pig with no one monitoring the situation. In the meantime, numerous people suffer “unknown” kidney and liver failures and await transplants, while sales continue.

**Quality assurance**

If an herbal remedy is effective, quality assurance is needed to ensure that the product has the expected effects. Quality assurance is also important if sufficient data is not available about its
efficacy. Quality implies certification in respect of authentication, standardization, composition, stability and safety. It also ensures that the herbal product is free from adulterants and contaminants. Authentication of some plants is difficult, because there is a need to adopt uniform binomial names for medicinal plants to eliminate confusion created by the common names. *Artemisia absinthium* Linn., for example, contains an active narcotic derivative, which can cause central nervous system disorders and generalized mental deterioration. This herb has at least 11 different common names (wormwood, absintium, absinth, absinthe, madderwort, wermuth, mugwort, magenkraut and herbal absinthii), 7 of which bear no resemblance with its botanical name (Patvardhan, 2004).

The potency of the active ingredients in herbal remedies is dependent on how and where herbs are grown, when they are harvested, how they are stored, what parts of the plants are used, and how these parts are extracted from the plant. Thus, there may be variation even within the same herbal remedy in terms of the amount and strength of the active ingredients (Maudlin, 1999). Standardization implies that the active ingredient must be identified to ensure that all brands and batches have the same amounts of working agent. This is impossible with the herbal medicines, because the constituents responsible for the claimed effects are often not identified. For example, Ma-haung (Ephedra) is a sympathomimetic agent that contains 5-6 different alkaloids. The alkaloid content varies (lot-to-lot variation) widely in commercial Ephedra containing preparations. In many other cases, we may have no idea about the constituents responsible for pharmacological activity. The constituents may seem to work synergistically and cannot be separated without loss of activity of the preparation. Because herbal preparations are used as crude mixtures, these are very difficult to standardize as allopathic medicines. In the absence of standardization, however, a number of herbs have become popular. For example, St. John’s Wort is used extensively for mild to moderate depression and some preliminary test has indicated no ill effects or interactions. Likewise, Saw palmetto has shown promising results when used for prostate problems. Garlic has been shown to have some beneficial effects on cholesterol levels; Echinacea for treatment and prevention of common cold; and Valerian for its calming and sleep-inducing effects (Youngkin & Israel, 1996).

Moreover, purity and adulteration of commercially produced herbal products have raised major questions. Varying concentrations of active ingredients in samples from same lot and same region can be encountered because of presence of contaminants and adulterants. For example, Echinacea, which is used as an immuno-stimulant is available in 3 species, *Echinacea angustifolia* DC., *E. pallida* (Nutt) Nutt and *E. purpurea* (Linn.) Moench. *E. purpurea* is adulterated with similar looking plant *Parthenium integrifolium* Linn. (Wild Quinine). These conditions also complicate the standardization process. Various adulterants and contaminants are given in Table 1. In addition, there are no specific standardization guidelines followed to ensure acceptable levels of impurities such as bacterial counts, pesticides, residual solvents and heavy metals. Moreover, quality assurance of herbal preparations should be mandatory because of intentional incorporation of drug substances. A recent study of herbal creams prescribed for dermatological conditions in the United Kingdom revealed that 8 of 11 preparations contained undeclared Dexamethasone at a mean concentration of 456 mg/g (Keane *et al*, 1999).
30 women treated with a Chinese herbal slimming preparation. These ladies died from renal failure in 1991-92. This happened with *Aristolochia* spp. one of the considered non-toxic herbs (Marwick, 1995). Potential adverse effects associated with some of the herbal drugs are summarized below (De Smet, 2002).

**Cardiotoxic herbs** — Aconite root tuber, cardioactive glycosides (digoxin, digitoxin, lanatoside, strophanthine), Liquorice root, Ma-haung (Ephedra) and Pokeweed leaf or root.

**Hepatotoxic herbs** — Green tea leaf, impila root, Ma-haung (Ephedra), kava rhizome, herbs rich in anthranoids, protoberberine alkaloids, coumarin, podophyllotoxin and toxic pyrrolizidine alkaloids.

**Neurotoxic herbs** — Aconite root tuber, *Alocasia macrorrhiza* Schott (Giant Taro) root tuber, Gingko seed or leaf, Indian tobacco, Ma-haung (Ephedra), Nux-vomica, yellow Jasmine rhizome, *Artemisia* species rich in santonin, essential oils rich in ascaridole and thujole, herbs rich in colchicine and podophyllotoxin.

**Renal toxic herbs** — Impila root, Jerring root and Pennyroyal oil.

It is difficult to determine which botanicals contain toxic substances that have acute adverse effects in a large fraction of users. It is more difficult; however, to recognize adverse effects that develop over long periods of time (e.g. hypokalemia from anthranoid laxatives).

### Table 1: Some adulterants and contaminants

<table>
<thead>
<tr>
<th>Types of adulterants &amp; contaminants</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botanicals (as adulterants)</td>
<td>Ailanthus, Phytolacca and Scopolia leaves substituted for belladonna; Xanthium leaves for stramonium and Dandelion for henbane, etc.</td>
</tr>
<tr>
<td>Microorganisms (as contaminants)</td>
<td><em>Staphylococcus aureus</em>, <em>Escherichia coli</em>, <em>Salmonella</em>, <em>Shigella</em>, <em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>Microbial toxins (as contaminants)</td>
<td>Aflatoxin, bacterial endotoxins</td>
</tr>
<tr>
<td>Pesticides (as contaminants)</td>
<td>Chlorinated pesticides, Organic phosphates, Carbamate insecticides and herbicides, Dithiocarbamate fungicide, Triazin herbicides</td>
</tr>
<tr>
<td>Fumigation agents (as contaminants)</td>
<td>Ethylene oxide, Methyl bromide, Phosphine</td>
</tr>
<tr>
<td>Toxic metals (as contaminants)</td>
<td>Lead, Cadmium, Mercury, Arsenic.</td>
</tr>
<tr>
<td>Drugs (as adulterants)</td>
<td>Analgesics and Anti-inflammatory drugs (e.g. amino-phenazone, phenylbutazone, indomethacine), Corticosteroids, Benzodiazepines, Warfarin, Fenfluramine, Sildenafil</td>
</tr>
</tbody>
</table>

(De Smet, 2002)
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occur idiosyncratically, or are readily ascribed to an underlying disease (e.g. hepatitis from the bile-duct remedy Celandine).

**Pharmacokinetic profile**

Establishing optimum dosage regimen in clinical situations is essential. It is very important to know the behaviour of a drug molecule once it is administered to a patient by various routes in various dosage forms. Determination of pharmacokinetic parameters helps to understand all the factors including inter-relationship between absorption, distribution, metabolism and excretion of drug and consequently the blood levels achieved. For a given dose of any herbal medicine, its physiological effect (or that of its constituents) will be governed by its bioavailability. Herbal medicines are complex mixtures. Therefore, oral or topical routes of administration are preferred. Knowledge of herbal pharmacokinetics can provide valuable information to aid practitioners in prescribing herbs safely and effectively. Pharmacokinetic data is important for understanding all possible interactions, viz. herb-drug interactions, herb-herb interactions, herb-food interactions and herb-disease interactions (Table 2) (Barnes et al, 2003; Fugh-Berman, 2000; Horowitz, 2000; Hussin, 2001). Pharmacokinetic information about herbal medicines is not readily available due to lack of scientific studies, inadequate reporting and improper documentation (Samanta et al, 2004). People do suffer complications due to the adverse effects of herbs or due to interactions. The extent of knowledge regarding the interactions, antagonistic or additive effects, within and between herbs

<table>
<thead>
<tr>
<th>Type of interaction</th>
<th>Ingredients</th>
<th>Consequences/risks</th>
</tr>
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<tbody>
<tr>
<td>Herb-herb interactions</td>
<td>Caffeine with Ginseng, Ginseng with Coumarins, Garlic with Coumarins,</td>
<td>Overstimulation and GIT upset, Bleeding episodes,</td>
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<td></td>
<td>Hawthorn with Digoxin</td>
<td>GIT upset, Bleeding episodes, Heart failure</td>
</tr>
<tr>
<td>Herb-drug interactions</td>
<td>Echinacea with corticosteroids, Ginseng with antidiabetics, Rosemary</td>
<td>Immunosuppression, Potentiation, Antagonism</td>
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<tr>
<td></td>
<td>with antidiabetics, Valerian with hypnotics, Dandelion with diuretics,</td>
<td>Potentiation, Antagonism</td>
</tr>
<tr>
<td></td>
<td>Aloe, Cascara, Rhubarb and Senna, etc. with antidiarrhoeals</td>
<td>Increased risk of hypokalemia, Antagonism</td>
</tr>
<tr>
<td>Herb-food interactions</td>
<td>Ginseng with tea, coffee, Digoxin and black liquorice, St. John’s wort with</td>
<td>GIT upset and overstimulation, Irregular heart rhythms</td>
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<td></td>
<td>aged cheese</td>
<td>and cardiac arrest, Fatal rise in blood pressure</td>
</tr>
<tr>
<td>Herb-disease interactions</td>
<td>Herbs with hypertensive properties, Herbs with hypo- or hyperglycaemic</td>
<td>Problem to patients with hypertension, Sudden fall/</td>
</tr>
<tr>
<td></td>
<td>activity</td>
<td>rise in blood glucose levels</td>
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</tbody>
</table>

(Barnes et al, 2003; Fugh-Berman, 2000; Horowitz, 2000; Hussin, 2001)
and conventional drugs is largely unknown. Besides the direct risks of adverse effects and drug interactions, there is an indirect risk that an herbal remedy may compromise/delay an effective form of conventional treatment.

The interactions are of greatest concern when patients are taking drugs with a narrow therapeutic window. In general, the most important drug-nutrient interactions to guard against include bleeding disorders (including bleeding in the brain), upsetting brain chemistry (serotonin syndrome, cholinergic syndrome, triggering bipolar disease, etc.), cardiac toxicity and hepatotoxicity (Mcneill, 1999).

**Efficacy of herbals**

Morphine is known to possess excellent analgesic activities with significant diarrhoea and cough relieving properties. This alkaloid, however, is no more prescribed because of its narcotic nature (Gutstein & Akil, 2001). Strychnine is the principle alkaloid present in Nux-vomica (*Strychnos nux-vomica Linn.*) seeds. Strychnine produces excitation of all portions of CNS. It is mainly used as an experimental tool to produce tonic-clonic seizures in mice (Klassen, 2001). *Ginkgo biloba Linn.* is another example, which is found to be beneficial in the management of Alzheimer disease. However, it is recently reported to precipitate epileptic seizures (Granger, 2001). d-Tubocurarine, obtained from *curare* plant is widely employed as an experimental tool to block nicotinic receptors competitively in laboratory preparations like frog rectus abdominis muscle (Bevan, 1994). Digoxin (LANOXIN) isolated from *Digitalis purpurea Linn.* is clinically prescribed for the treatment of congestive heart failure (Uretskey et al, 1993). Vinchristine (ONCOVIN) and vinblastine (VELBAN), the alkaloids obtained from *Catharanthus roseus G. Don* syn. *Vinca rosea* Linn. are popular for their anticancer activity (Noble et al, 1958). Emetine, isolated from ipecac is therapeutically used to produce emesis particularly in case of over dosage or accidental poisoning. Atropine (BELLPINOATRIN) is a favourite drug of gastroenterologists for relieving spastic pain and glaucoma (Tryba & Cock, 1997). Colchicine (GOUTNIL) obtained from *Colchicum autumnale Linn.*, is a popular antigout agent among the elderly patients (Zemer et al, 1991). Reserpinine (SERPASIL) obtained from *Rauwolfia serpentina Benth. ex Kurz* was enthusiastically introduced into Indian market as an antipsychotic and antihypertensive agent. However, due to increased suicidal tendencies observed with this drug, it's use is now confined to laboratory as a depletor of monoamines (Schuldiner, 1994). Codeine (COREX), isolated from *Papaver somniferum Linn.*, is used as an anti-tussive agent (Caraco et al, 1999). Neurobiologists and phytochemists are now exploring the possibility of isolating some hormones like estrogens, testosterone, etc. from plant
Herbs are generally safe if used with proper knowledge, but they can be harmful and even fatal if misused (Studdert et al, 1998; Senior, 1998). Bleeding disorders can be caused by any herb that contains a significant concentration of ingredients possessing anticoagulant property (such as Red clover and Dong quai containing coumarins) when taken concurrently with anticoagulant medications (such as Warfarin, Coumadin, Clopidogrel, etc.).

One of the most serious risks associated with herbal medicines is the fact that consumers mistakenly assume that because herbs are natural, they are safe.

The potency of the active ingredients in herbal remedies is dependent on how and where herbs are grown, when they are harvested, how they are stored, what parts of the plants are used, and how these parts are extracted from the plant. Thus, there may be variation even within the same herbal remedy in terms of the amount and strength of the active ingredients.

Some of the herbs have different common names and different herbs have similar appearance so authentication becomes a necessity. The possibility of presence of adulterants and contaminants can not be ruled out.

Tips/Warnings for healthy use of herbal medicines

- Herbs are generally safe if used with proper knowledge, but they can be harmful and even fatal if misused (Studdert et al, 1998; Senior, 1998).

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Ginkgo biloba and Devil’s claw
have also been shown to cause bleeding disorders in humans, sometimes in the absence of concurrent anticoagulant medication use. Feverfew (a herb used to treat migraine headaches), ginger, turmeric and white willow extract may also induce a mild anticoagulant effect, but till date, bleeding disorders have not been shown to occur to an appreciable degree in humans (Mcneill, 1999; Rosenblatt & Mindel, 1997; McRae, 1996; Matthews, 1998).

- Popular herb St. John's Wort helps in relieving mild to moderate depression, but do not mix it with prescription antidepressants, especially the serotonin reuptake inhibitors such as Prozac, Serzone, Luvox, Paxil and Zoloft. This is a case of getting too much of a good thing, which can be harmful.

- Herbal supplements that elevate acetylcholine concentrations in the brain (huperzine A, *Bacopa monnieri* (Linn.) Penn., phosphatidylserine, acetyl-L-carnitine, DMAE-dimethylamino ethanol) have the potential to cause cholinergic syndrome, if taken concurrently with anti-Alzheimer's drugs (such as acetylcholinesterase inhibitors - Donepezil, Tacrine) (Janetzky & Morreale, 1997; Bladt & Wagner, 1994).

- The herbal agent hawthorn works in the body in a similar fashion as other cardiac glycoside drugs, such as Digoxin.

- Echinacea, which fires up the immune system, does not mix well with corticosteroids or any other drug that suppresses the immune response (Mcneill, 1999).

- Combining Valerian with prescription and non-prescription sleep aids and/or alcohol can create a dangerous state of oversedation.

- Another subtle but real risk involves pregnant women and nursing mothers who take herbal medicines and pass it on to the child through breast milk. There are hardly any studies on the teratogenic effects of herbal remedies. There is little knowledge of the effects of herbal medicines on the developing fetuses (Delaney, 1997).

Conclusion

In India, we have several systems of medicine, viz. Nature cure, Ayurveda, Homeopathy, Siddha and Unani being actively practiced in different parts of our country. When a patient gets seriously ill, he desperately desires relief from discomfort at the earliest irrespective of the system of medicine. In other words, he is open to accept any medication, if relief is guaranteed. In such a situation, we as Indians are best placed to work out an integrated system of medicine taking advantage of both, modern technology and traditional therapies. Moreover, clinicians should never recommend herbal remedies without sufficient evidence of their safety backed by rigorous study. Toxic effects of herbs are often not the fault of herbs, but are caused by products containing misidentified plants or contaminants such as bacteria, heavy metals or even prescription drugs. The authors are of the view that before marketing, herbal remedies must undergo well-planned animal studies and ethical clinical trials so as to establish their therapeutic value.

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