Safety of medicinal plants

Inamul Haq
Ex-Drug Controller, Ministry of Health, Government of Pakistan, Islamabad

SUMMARY

The last decade has witnessed a great revival of interest in the use of herbal medicines both in the developed as well as developing countries. Almost 50% of the medicines we use today are derived straight from plants and 25% of the prescription drugs have their genesis of tropical plants. According to WHO, 80% of the world population rely chiefly on plant based traditional medicines specially for their primary health care needs. The common belief based on tradition, that medicinal plants being "natural" or near to nature are always safe, is not held to be true lately. The advancement of technology has enabled the scientists to detect minute amounts of carcinogenic and toxic chemicals in these herbs and recognize or evaluate potentially hazardous effects of some of the herbs used in traditional medicines since centuries. This article aims to highlight the side effects and adverse reactions/interactions of few most commonly used herbs considered to be safe since centuries with an advise to the physicians and pharmacists to consider the health hazards associated with the use of such drugs while taking the history of the patients.

INTRODUCTION

Though medicinal plants have been used since antiquity for the prevention and treatment of various ailments, lately there has been a great resurgence in the use of herbal remedies specially during the last decade and a half. At the turn of the century, approximately 170 herbal drugs were officially recognized in the U.S.P and N.F. The Director of WHO, Traditional Medicine reported in 1993 that 80% of the world population rely chiefly on traditional medicine, mainly plant based, specially for their primary health care needs. International Scenario.

America

In America, the annual market value of phytomedicine was reported to be $1.5 billion in 1994 which has grown enormously over the years. It is estimated that in 1997, Americans spent $3.2 billion on herbal medicines like Gingko biloba for memory problems and Achinacea for colds and flu in spite of the fact that herbal medicines are inadequately regulated by the FDA. According to FDA survey, 16 million Americans are using medicinal herbs actively. Herbal medicines continue to be a major market in US pharmacies and constitute a multi billion dollar industry selling approximately 1500 botanicals and dietary supplements or ethnic traditional medicine.

Europe

Europe is reported to have the highest turnover in herbal medicines with a retail sales volume of $6 billion per annum.

United Kingdom

In UK, around 5500 herbal products were available in 1980 on the pharmacies or on the general sales list out of which 1000 products derived from 550 herbs were estimated to be marketed with product licenses. The sales of herbal medicines in the U.K increased by 25% between 1990-1995 over the last years.

Germany

The German herbal medicines market was worth $1.7 billion in 1989 equal to 10% of the total pharmaceutical market which surpassed $2.0 billion by 1998. Over 70% of German Physicians either prescribe medicinal herbs or refer their patients to traditional practitioners. The cost of about 40% of the herbal remedies prescribed by the German Physicians are covered by the health care system.

China

In China, the total production of herbal medicines was $2.3 billion in 1995 showing an increase of 212.6% compared with 1990. Herbal medicines represented 33.1% of the total drug market in 1995. Botanicals are used for the primary health care needs of 40% of China’s urban patients and over 90% of its rural patients.
In Japan, sales of herbal medicine products are estimated to be \(2.1\) billion per year constituting about \(4.0\%\) of the total market for pharmaceutical products. In Tokyo, \(49\%\) population had used herbal medicine in 1990 according to a survey. Per capita consumption of herbal medicines is reported to be the highest in Japan.\(^7\)

**Table-1 shows the Worldwide Phytomedicine Market, 1994**
(Per Dr. Grunwald. Phytopharm. Phytotherapeutics market)

<table>
<thead>
<tr>
<th>Country</th>
<th>Million US $ @ Retail</th>
</tr>
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<tbody>
<tr>
<td>European Union</td>
<td>6,000</td>
</tr>
<tr>
<td>Rest of Europe</td>
<td>500</td>
</tr>
<tr>
<td>Asia</td>
<td>2,300</td>
</tr>
<tr>
<td>Japan</td>
<td>2,100</td>
</tr>
<tr>
<td>North America</td>
<td>1,500</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12,400</strong></td>
</tr>
</tbody>
</table>


**Malaysia**  
In Malaysia, the market for traditional medicine is estimated to be M $ 1.0 billion to M $ 2.0 billion annually, which is larger than the market for modern medicine.\(^11\)

**Ghana**  
In Ghana, 70% population rely on herbal medicines where the Practitioner: Patient ratio is 1:400 in case of traditional medicine as against 1:12000 in modern medicine.\(^12\) Fig 1 shows the Percentage of the population using Traditional Medicines, Selected Countries in The Western Pacific Region.

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**Viet nam**  
A survey conducted in 1997 showed that 50% of the population preferred to be treated by traditional rather than modern medicines. Traditional medicine is practiced at all levels of health care i.e. primary, secondary and tertiary.\(^7\)

**Republic of Korea**  
In the Republic of Korea, annual sales of herbal medicines was reported to US $543.5 million in 1996. According to the Ministry of Health document, in 1997 there were reported to be 300 herbal pharmaceutical companies, 13733 herbal medicine dealers, 820 wholesalers and 10751 drug stores dealing with herbal medicines in the country.\(^7\)

**Philippines**  
In the Philippines, combined sales of four government and one private herbal medicines manufacturer in 2000 were about US $ 10 million.\(^7\)

**India**  
In India 70% of populations are reported using traditional medicine for primary health care. The present annual turnover of herbal medicinal products manufactured by large companies is estimated to be approximately US $ 300 million, compared to a turnover of approximately US $ 2.5 billion for modern drugs.\(^{13a}\)

**Pakistan scenario**  
Traditional healers (Hakims/Tabibs) are Registered by the Govt. under an Act of the Parliament but there is no regulatory control on the manufacture, sale, distribution etc. of traditional medicines. There are around 46,000 Registered "Hakims" and about 74,000 Registered Homeopaths\(^{14}\) as against some 102516 Registered Physicians. The number of recognized Tibbia Colleges and Dispensaries is 28 and 315 respectively.
Safety of medicinal plants

Tibbi Pharmacopoeia published by the National Council of Tibb lists about 900 single herbs\(^\text{15}\) whereas Hamdard Pharmacopoeia of Eastern Medicine lists 186 single vegetable drugs used exclusively in "unani medicine".\(^\text{16}\) According to information collected in 1982, around 200 medicinal plants were found to be extensively used by the traditional healers in their day-to-day practice as evidenced by their Annual Consumption by ten leading "Dawakhana's" (herbal drug manufacturers) in Pakistan.\(^\text{17}\) As can be seen from above, the worldwide interest in herbal medicines has grown tremendously in the last decade or two.

Factors promoting use of herbal medicines

Amongst several factors contributing towards the potential use of herbal drugs, holistic approach to the health problems, safety, lack of adverse reactions and side effects have been mostly found to particularly influence the use of such medicines in the developed countries whereas their accessibility, affordability, historical and cultural background besides the above factors promote their use in the developing countries. Added to these strengths and the clinical evidence of safety provided by some herbal drugs, traditional herbal therapies have no doubt the potential to increasingly contribute to a better health care system in many countries.\(^\text{15}\) Fig. 2 shows the evidence of Safety for some Herbal Medicines.

![Figure 2. Good evidence of efficacy exists for some herbal medicines- but evaluation is inadequate](image)

Percentage of randomized clinical trials (RCTs) showing benefit of herbal medicines (based on 50 RCTs with 10 herbal medicines for 18 therapeutic indications)


Herbal drugs— not always safe

There is a general belief amongst the consumers all over the world that herbal drugs are always safe because they are "natural" or near to nature but evidence suggests otherwise.\(^\text{19-20}\) The mere fact that a product is "natural" does not signify that the product is safe, says Carol. A. Newall, the British Co-author of Herbal Medicine: A Guide for Health Care Professionals. According to him, naturalness does not by definition guarantee harmlessness nor does the general belief that herbs used since decades or centuries provide enough evidence of their safety.\(^\text{21}\) Although limited evidence suggests that adverse effects associated with the use of herbal drugs are less likely to occur than with conventional drugs, they do occur though usually mild and only effecting a small number of people. A recent evidence suggests that some of the herbs considered to be safe over the last many decades have proven to be associated with health hazards. The English translation of The Complete German Commission E Monographs lists more than 100 ineffective or toxic herbs that have been used medicinally, but are no longer recommended.\(^\text{22}\) The advancement of technology has enabled the scientists to detect minute amounts of carcinogenic and toxic chemicals in these herbs and recognize or evaluate potentially hazardous effects of some of the herbs which had been used in traditional medicine since centuries. Though any organ system can be affected, the most common adverse effects involve the skin, liver and gastro-intestinal tract. There is a long list of medicinal plants used traditionally that are lately reported to be hepatotoxic,\(^\text{23-24}\) a classical example being of Germander that had been used with apparent safety for centuries. It was only in 1990's that this plant was first identified to be a hepatotoxic drug.\(^\text{23}\) Similarly many plants have been identified to be renotoxic. In Belgium several preparations based on Chinese plants were reported to be responsible for 70 cases of renal impairment\(^\text{26}\).

Animal experiments, though not supported by human experiments, have also shown that some common herbs/medicinal plants like Hollarrhena anti dysenterica, Aegle marmelos and Terminalia chebula used in traditional medicine since centuries in Pakistan have lately been reported to produce hepatic lesions while Terminalia chebula and Withania somnifera gave rise to marked renal lesions.\(^\text{27}\) Another commonly used herb—Embelia ribes had been reported to cause visual defects and eventually optic atrophy in animal experiments.\(^\text{28}\)

Side effect/ad reactions & interactions of some common herbs

Following are some of the examples of side effects/adverse actions and interactions associated with the use of common herbal drugs used in traditional medicine routinely since centuries.
a) **Liquorice**: Traditionally liquorice root has been used to treat many ailments including asthma, stomach and duodenal ulcers, singles (caused by a Herpes virus), arthritis, chronic depression etc. Lately however it has been observed that one of the active ingredients, glycyrrhizic acid, when taken in large quantities, can promote sodium and water retention as well as potassium depletion, making it risky for people with blood pressure, kidney or heart disease. Potential unwanted effects include edema and hypertension due to excessive use. To avoid these problems, liquorice root should not be taken continuously as a tea, tincture or in tablet for more than 4 to 6 weeks.\(^5\) Liquorice is a common ingredient of classical household cold and flu preparation! remedy, "JOSHANDA" used in Indo-Pakistan subcontinent.

b) **Ephedrm**: The herb has been used in traditional Chinese medicine since antiquity for the treatment of respiratory ailments. The drug has been advertised as a supposedly safe, natural product for weight loss, body building and mood evaluation. Recently the drug became highly controversial due to its use in slimming formulas and products claiming to deliver a "legal high" resulting in serious health hazards. According to FDA, there has been 15 deaths attributed due to the intake of ephedra based drugs since 1990 necessitating legal restrictions on the duration and dose of such drugs.\(^5\) According to another report, the drug has been blamed for 20-30 deaths and 800 adverse reactions since 1993.\(^3\) Ephedra has many side effects including restlessness, irritability, increased blood pressure and heart rhythm disorders. The alkaloid ephedrine contained in ephedra herb can cause serious toxic reactions ranging from liver damage to severe high blood pressure and heart problems when taken with MAO and also with ergot alkaloid derivatives or oxytocin, cardiac glycosides,halothane, guanethedine.\(^22\) Due to its many side effects and adverse reactions, the herb should not be taken with any MAO-inhibitors (monoamine oxidase inhibitors, such as those in some antidepressants) or heart or blood pressure medications Pregnant women should avoid ephedra because it induces uterine contractions.\(^5\) Many herbal cough preparations marketed in Pakistan contains ephedra as one of their ingredients.

c) **Aloe vera**: Seventh most widely used herb for centuries as a treatment for minor bruises and is increasingly being used in products for internal consumption. Long term use of aloe latex could results in potassium deficiency so the laxatives containing anthraquinone glycosides should not be used continuously for longer than 1-2 weeks owing to the danger of electrolyte imbalance.\(^29\) Certain medications can interact positively or negatively with the glycosides contained in the drug.\(^29\)

d) **Sassafras**: The herb has been used in traditional medicine since centuries in North America for the treatment of rheumatism, arthritis, cold and flu. The root bark contains small amount of a potent carcinogen toxic to liver if taken in large quantities or over extended period of time.\(^5\)

e) **Ginkgo biloba**: Ginkgo fruits and seeds have been used medicinally for thousands of years. Extract of the plant is an OTC herbal drug marketed in many countries including Pakistan (under the name CRATEX), as a supplement to improve mental alertness and related memory problems. Researchers have shown that the extract is a potent inhibitor of platelet-activating factor and long term use has been associated with increased bleeding time, spontaneous hemorrhage and sub dural haematomas.\(^31\) Adverse reactions that have been reported to WHO include hypertension, leucopenia, thrombocytopenia and hallucinations.\(^32\)

f) **Senna**: Senna, another so called weight loss herbal drug used traditionally for constipation, can have adverse effects on the heart because regular consumption is reported to deplete the body of potassium causing fatalities. Other adverse reactions include grand mal seizures, circulatory failure, hypertension and anaphylactic reaction.\(^32\)

g) **Sil ybum marianum**: Silymarin obtained from the herb and widely promoted as a liver tonic, has been associated with cerebral hemorrhage, hepatic coma and neuropathy.\(^32\)

h) **Ginseng**: Fourth most widely used Chinese medicinal herb for the treatment of a variety of conditions since times immemorial, Ginseng is used as a general tonic and is claimed to increase body's resistance to stress and builds up general vitality besides treating hypertension, diabetes, depression.\(^4\) Lately the herb has been reported to cause hypertension and mastalgia as documented side effects.\(^31\) Taking Ginseng may keep blood thinners from working correctly resulting in problems with blood clotting.\(^34\) Some recent reports have also linked ginseng to potential medication interactions with warfarin and digoxin. Taking Ginseng and Digoxin together may cause an increase in Digoxin levels in the blood, leading to Digoxin poisoning.\(^35\) Ginseng and antidiabetic drugs taken together may make blood sugar too low leading to blurred vision, tremor (shaking), hunger, sweating, headache, skipped heart beats, confusion, nervousness and extreme tiredness.\(^36\) Ginseng is reported to interact with many other drugs which include steroids, anti
 depressants, water pills, estrogens etc. Excessive doses of ginseng have been reported to cause agitation, insomnia and raised blood pressure.

j) Alfa alfa: The herb widely used in Homeopathy, is said to contain vitamins A,C,E and K as well as calcium, potassium, phosphorus and iron. However it has been reported that the use of this herb can induce systemic lupus erythematosus (SLE) like syndrome in individuals predisposed to this condition.32

k) Comferey: The herb was used by Greek Physicians in the first century as a safe drug in the form of poultice to heal wounds and as a tea to help knit broken bones. In late 1970,s scientists discovered that it contains pyrrolizidine alkaloids which are known to be hepatotoxic and has been associated with obstruction of blood flow to the liver, possibly leading to hepatotoxic reactions32 besides being a risk for cancer. Products containing comfrey should not be taken internally and the topical application of comfrey containing preparations to broken skin should be avoided.32

l) Aconite: Aconite alkaloids contained in the root-stocks of plants of Aconitum family are accredited with analgesic and anti-inflammatory effects within several systems of traditional medicine and are still widely proposed for the treatment of rheumatism, neuralgia and cardiac complaints. However aconite poisoning is common. In China alone it has been reported that over 600 cases of aconite poisoning have been attributed to the use of these substances in herbal medicines over the past 30 years up to 1995.41

m) Ispaghula: Ispaghula which is considered to be the safest and largely used for its demulcent and laxative properties since centuries is reported to have adverse reactions including bronchospasm, asthma and intestinal obstruction. If swallowed dried it may cause oesophageal obstruction.32

n) St. John’s wort: An anti depressant and dietary supplement has a potential market in Europe and America. The German doctors are prescribing millions of daily doses and the value of prescriptions for this anti-depressant drug is reported to be twice that of latest Allopathic drug-PROZAC.42 A study conducted by the N.I.H in USA however showed a significant drug interaction between St. John’s wort and Indinavir, a protease inhibitor used to treat infection.43 Based on these results, it is expected that the herb may significantly decrease blood concentration of all the currently marketed HIV protease inhibitors (PIs) and possibly other drugs.

Table 2 summarizes the general Side Effects and Adverse Reactions/ Interactions of some selected Herbal Drugs Based on Clinical evidence.

<table>
<thead>
<tr>
<th>Medicinal plant</th>
<th>Side effect/ad. reaction &amp; interaction</th>
</tr>
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<tbody>
<tr>
<td>Liquorice</td>
<td>Glycyrrhizinic acid promote sodium and water retention &amp; potassium depletion- risky for people with B.P, Kidney aI1c1 Heart diseases.</td>
</tr>
<tr>
<td>Ephedra</td>
<td>Insomnia, restlessness, irritability. Since 1993 responsible for 20-30 deaths and 800 adverse reactions. Can cause toxic reactions when taken with Monoamine oxydase inhibitors and some other drugs like ergot alkaloid derivatives, oxytocin, guanethedine etc.</td>
</tr>
<tr>
<td>Aloe vera</td>
<td>Aloe latex could result in potassium deficiency thus endangering electrolyte imbalance.</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Potent inhibitor of platelet-activating factor- long term use associated with increased bleeding time. Adverse reactions including hypertension, leucopoenia, thrombo penia and hallucinations</td>
</tr>
<tr>
<td>Sylibum marianum</td>
<td>Silymarin associated with cerebral hemorrhage, hepatic coma and neuropathy.</td>
</tr>
<tr>
<td>Ginseng</td>
<td>May create blood clotting problem. Potential medication interaction with Warfarin, Digoxin, Anti diabetic and other drugs.</td>
</tr>
<tr>
<td>Comferay</td>
<td>Hepato-toxic.</td>
</tr>
<tr>
<td>Aconite</td>
<td>Acute poisoning</td>
</tr>
<tr>
<td>Ispaghula</td>
<td>May cause bronchospasm, asthma and intestinal obstruction.</td>
</tr>
<tr>
<td>St. John's wort</td>
<td>Significant interaction with Indinavir-a protease inhibitor and, some other drugs.</td>
</tr>
</tbody>
</table>
Many different and not very significant interactions can occur between herbs containing large amounts of mucilage including Aloe, Flaxseed (Linum usitatissimum), Ispagula. These herbs may slow the absorption of any drug when taken orally at the same time. To avoid any absorption problem, it is advisable to take the herb and the drug at least several hours apart.

Interactions are likely to cause problems in case of herbs reported to possess cardiac, anti diabetic, diuretic, sedative, hypertensive, hypotensive or anti coagulant effect.

Many medicinal herbs known to lower blood sugar levels which include Momordica charantia (Karela), Gymnema sylvestre (Gurmar) and Pterocarpus marsupium (Indian Kino tree) when combined with Insulin could result in hypoglycemia. To avoid this, it is necessary to constantly monitor blood sugar levels and make necessary adjustments in the dosage of insulin accordingly.

Some most popular herbs like Garlic (Alium sativum), Ginkgo biloba, Ginger (Zingiber officinalis), Ginseng, Fever few (Tanacetum par.) are known to delay the blood clotting time. So if the patient take anti-coagulant drugs like OTC aspirin or the potent prescription drug Warfarin, he should use these herbs after checking with his doctor because they are likely to cause hemorrhage.44

Several cases of bleeding involving anti-coagulant therapy and herbals have been reported. The American Society of Anaesthesiologists has issued warnings against using herbals such as ginger, ginkgo, kava kava and St. John’s wort before undergoing surgery because these herbs may cause increased risk of bleeding or prolong the effect of anesthesia.45

Need for regulatory controls on herbal drugs

These are some examples of problems apparently associated with the uncontrolled use of "natural" products and traditional herbal medicines. It needs to be mentioned here that most serious side effects originates from overuse or misuse of such medicines. The likelihood of side effects increases when the production and sale of such products is largely uncontrolled and or unregulated and the consumer is not adequately informed about their proper uses. While in some countries herbal medicines are regulated through official controls and rigorous manufacturing standards, this is not so everywhere. In Germany, for example, where herbal products are sold as "phytomedicines" they are subject to the same criteria for their safety, efficacy and quality as applicable to other drugs.46 Regulatory controls are therefore considered necessary to safeguard

Drug interactions with herbal drugs have not been adequately researched but there are increasing number of case reports of herbal-drug inter actins in literature.

Under the National Toxicology Program, studies are underway in USA to the potential of herb/ herb and herb/drug interactions and the clinical responses of some sensitize populations such as pregnant women, the young, the developing fetus, the elderly etc. using herbal products.

As the clinicians and scientists gain experience with using medicinal herbs, it is likely that other side effects and interactions comes to light. So it is always wise to consult a qualified medical practitioner having clinical herbal experience in case of any doubt about the compatibility of herb and the drugs you intend to take.

Role of physicians and pharmacists:

Physicians generally do not ask the patients about having used herbal preparations while taking their history. But because of the biological potency, side effects and adverse reactions of many of the herbal preparations and their increasing popularity and availability, it is necessary that patients should be asked specifically about their use, especially when presenting with unusual symptoms or signs while prescribing any allopathic medicine. Apart from the role the physicians have to play in safeguarding the public health, pharmacist's interventions in the appropriate use of herbal medicines are necessary to make the overall health delivery system safe and effective. Pharmacists should therefore be

### SIDE EFFECTS/ADVERSE REACTIONS & INTERACTIONS BASED ON ANIMAL EXPERIMENTS

<table>
<thead>
<tr>
<th>MEDICINAL PLANT</th>
<th>SIDE EFFECT/ A. REACTION &amp; INTERACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Hollarrhena antidys. Aegle marmalos Terminalia chebula</td>
<td>Hepato-toxic</td>
</tr>
<tr>
<td>2) Terminalia chebula Withania somnif.</td>
<td>Reno-toxic</td>
</tr>
<tr>
<td>3) Embelia ribes</td>
<td>Visual defects leading to optic atrophy.</td>
</tr>
</tbody>
</table>
knowledgeable about the medicinal plants, herbal therapies and other herbal based dietary supplements in view of their increasing popularity and utilization so as to be able to provide objective information to the consumers.

Some important sources, among others, that provide detailed information about herbal drugs/products are:

a. WHO Adverse Drug Reactions Database, Uppsala, Sweden.
c. Traditional Medicine Program. WHO - Geneva, Switzerland.
d. NAPRAalert (Natural Product ALERT) database (computerized database on the medicinal uses of natural products, especially plant profiles) USA.
e. English translation of the German Commission E monographs published by the American Botanical Council.

REFERENCES

10. 9a. Encyclopedia of Medicinal Plants. BY CHEV ALLIER.
17. Tibbi Pharmacopoea Published by the National Council of Tibb.
35. WHO Adverse Drug Reaction Database. Uppsala Sweden.