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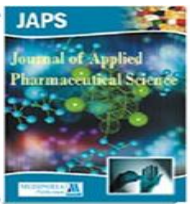

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Concerns regarding the safety and toxicity of medicinal plants - An overview

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ABSTRACT

All over the world, especially in developing countries herbal drugs are playing an important role in health care programmes.This is because they are being cheap and locally available. There is a general belief amongst the consumers globally that herbal drugs are always safe because they are “natural". However evidences suggests otherwise. The mere fact that a product is "natural" may not signify that the product is safe. Although limited evidence suggests that adverse effects associated with the use of herbal drugs are less likely to occur than with conventional drugs, theydo occur though usually mild and only affecting a small number of people. 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. Herbal remedies can act either as agonists or antagonists that potentiate some drug therapies. Therefore , an understanding of conventional drugs is an essential prerequisite for effective herbal therapeutics.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.

Key words: Safety and Toxicity, herbal medicines/ drugs, side / hazardous effects, Pharmaceuticals, Botanicals, Allergic, Contamination & adulteration

INTRODUCTION

Medicinal plant species which are being used, for treatment of particular diseases,on large scale, are reported to be having serious side effects. Many drugs have originated from biologically active plant chemicals, and their medicinal uses are attributed to various active chemicals found in them. The major difference between using a medicinal plant and a chemical drug is that most conventionally trained doctors with no formal training in plants which is of great concern to the common man. Synthetic drugs usually consist of a single chemical, while medicinal plants can contain complex mixture of 400 or more chemicals. It’s comparatively easy to figure out the activity and side effects of a single chemical, but there is just no way scientists can map all the complex interactions and synergies that might be taking place between all the various chemicals found in a plant, or crude plant extract containing all these chemicals which is used traditionally . It is not unusual for a plant to contain a single documented cancer-causing chemical and also maybe five other chemicals that are anticancerous and which may counteract the one chemical having toxic effects. Overall, the plant extracst may even provide some type of anticancerous effects. The vast majority of medicinal herbs contain dozens of different compounds of great complexity, often mucilages, tannins, polysaccharides etc. that may modulate and modify the effects of any "active principles".

Studies have shown that effects produced by extracts of whole plants cannot be mimicked by administering isolated purified constituents of the plant(Philomena et al 2009).

India and China are two of the largest countries in Asia, which have the richest arrays of registered and relatively well-known medicinal plants. The Indian subcontinent is well known for its diversity of medicinal plants, forest products and the age-old healthcare traditions, there is an urgent need to establish these traditional values in both the national and international perspectives realizing the ongoing developmental trends in traditional knowledge and side effects caused by these medicinal plants (Wu, Y. 1988).

Those people who are already involved in pharmaceutical therapies seeks herbal medical treatment more often. In many cases, herbalists would not treat the primary presenting symptom undergoing drug treatment - be it ulcers treated with Zantac or cardiac arrythmia treated with Digoxin - but rather concentrate on supporting other systems and functions stressed by the primary symptom. This allows the body to recover because of healing potential of the herbals. These capabilities are directed toward repairing the presenting condition. In other cases, it can be a priority to wean someone off drugs, e.g. steroids, in case of steroids, supportive therapy to restore adrenal function is vital. (Ernst, 2007**)**.

Safety and Toxicity of herbal medicines

The explanation of "toxic" is ultimately a matter of viewpoint. Many ordinary foods contain constituents that could be allergic or considered as toxioc such as the alpha gliadin produced by gluten in wheat,oats and rye, the cyanogenic glycosides in many fruit seeds, the thiocyanates of the Brassica vegetables, alkaloids of the Solanaceae and lectins of many pulses including soya and red kidney beans. These foods are generally regarded as safe throughout the world . Similarly, both life saving items such as water and oxygen - can kill in excessive, amounts, so the quantity is often an important consideration.(Boullata,and Nacen 2000; Ernst, 2007).

However, in practice, from a safety point of view three groups of herbs can be identified. In the first group , there are a handful of herbs that contain near pharmaceutical concentrations of poisonous constituents which should on no account be taken internally by unqualified persons except in homeopathic potencies. Examples are *Atropa belladonna, Arnica spp, Aconitum spp,,Digitalis spp* (Mcrae, 1996). In the second group , are herbs with very powerful actions, often causing,nausea or vomiting. They are perfectly safe used under appropriate conditions. Examples are,*Lobelia and Eonymus spp.*

Certain contradictions can be seen in different countries . viz., *Ephedra i*s restricted, in the UK, perhaps with justification, but is available freely in the US. In the third group , with some scientific support, there is an idiosyncratic grouping of herbs which exhibit specific kinds of toxicity. The hepatotoxicity of pyrrolizidine-alkaloid-containing plants such as Comfrey *(Symphytum*) the best known among these.. *Dryopteris* (Male Fern), *Viscum* (Mistletoe) and *Corynanthe* (Yohimbe) can be quoted as other examples. Laymen are advised to avoid internal consumption of these herbs.

Side effects & 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.

Table 1. Comparison of adverse reactions in pharmaceuticals and botanicals**.**

Pharmaceuticals	**Botanicals (Dietary Supplements)**
Adverse drug reactions to pharmaceutical medications were responsible for more than 100,000 fatalities per year, while non-fatal adverse reactions serious enough to warrant hospitalization were reported for approximately 2.2 million cases (Lazarou, 1998). These statistics apply only to adverse drug reactions in which the medication was appropriately used.This places adverse reactions to pharmaceuticals as the fifth leading cause of mortality in the U.S.	Reported fatalities from adverse reactions to botanical supplements range from less than 12 to 24 (at most). Adverse reactions to dietary supplements are not as well monitored as for pharmaceuticals. Even allowing for under-reporting, however, the documented number of serious or life-threatening adverse reactions to botanical medicines remains extremely low. For current information on adverse events reported to the FDA, visit the FDA Center for Food Safety and Applied Nutrition.

(Courtesy to Reports from Uni. of Minnesota 2009)

Toxic ingredients

Botanical supplements containing toxic constituents, such as liver toxins or carcinogens (chemicals with potential to cause cancer), do occasionally cause adverse reactions, but as a rule, these supplements are quickly withdrawn from the market once a potential problem has been identified. Some may still be sold in supplements imported from Asia or Europe.

The following is a partial list of botanicals with potentially toxic constituents: *Aconite, Alfa alfa* , *Aloevera*, Borage, Calamus, Chaparrel ,Coltsfoot, Comfrey ,Ephedra, Germander , *Ginkgo biloba, Ginseng, Glycyrrhiza glabra (*Licorice) *Isapghul, Sassafras* , Senna , *Silybum marianum* , St. John's wort etc. A few of the above are briefly covered below.

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.

***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 Erythromatosus (SLE) like syndrome in individuals predisposed to this condition.

Aloevera: 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.

Certain medications can interact positively or negatively with the glycosides contained in the drug.

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 reactions besides being a risk for cancer.

Ephedra: 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. 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.

***Ginkgo biloba*:** *Ginkgo* fruits and seeds have been used medicinally for thousands of years 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 (Rowin and Lewis, 1996).

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, (Punnonen and Lukola 1980). Lately the herb has been reported to cause hypertension and mastalgia as documented side effects. Taking Ginseng may keep blood thinners from working correctly resulting in problems with blood clotting (Becker, 1996).

Isapghul: Isapghul 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.

Liquorice (*Glycyrrhiza glabra*): if we look at use of liquorice from a western perspective, we see that its use has changed little over 3,000 years. 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. It has demulcent (soothing to irritated membranes), expectorant properties, and also stimulates mucous secretions of the trachea. Other activities include significant anti-inflammatory effects, a protecting effect on the liver against toxic substances and anti-allergic activity. Earlier research reports have shown that glycyrrhizin stimulates the excretion of hormones by the adrenal cortex. Lately however it has been observed that one of the active ingredients, glycyrrhizinic 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. *(*DHom John Claydon, 2010)

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.

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.

Silybum marianum*:** Silymarin obtained from the herb ***Silybum marianum and widely promoted as a liver tonic,has been associated with cerebral hemorrhage, hepatic coma and neuropathy.

St. John's wort: An anti depressant and dietary supplement has a potential market in Europe and America. A significant drug interaction between St. John's wort and Indinavir, a protease,inhibitor used to treat infection was reported in a study, conducted by the N.I.H in USA. Based on these results, it is expected that the herb may significantly decrease blood Concentration(FDA Guide lines)

Need for regulatory controls on herbal drugs

Most serious side effects originate 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. Regulatory controls are therefore considered necessary to safeguard Drug interactions with herbal drugs. 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 (WHO Reports, 1997, 2002).

The current emphasis is on screening the environment for man-made genotoxic and carcinogenic compounds .They detracts from studies on the possible health hazard or beneficial effects of naturally occurring agents to which humans are daily exposed in their day to day life . The simple phenolics, belong to this category of compounds. They are ubiquitous among plants, used as food

additives, and ingested daily in milligram quantities. They are also known to induce double-strand DNA breaks, DNA adducts, mutations and chromosome aberrations in a great variety of test systems. However, both *in vitro* and *in vivo* assays have proved that they can suppress the genotoxic activity of numerous carcinogenic compounds. Some studies on animal models revealed that, phenolics induce precancerous lesions, papillomas and cancers, act as cocarcinogens, and exert a promoting effect in various rodent assays. At the initiation and promotion stages induced by carcinogens and promoters of different molecular structures. phenolics have proved to be potent inhibitors of carcinogenesis . The extent to which a health hazard or protective activity of complex dietary mixtures is due to their phenolic content needs to be confirmed by further research. In addition, these multiple, occasionally contradictory functions of simple phenolics make it difficult to propose their use as chemopreventive agents (Stich 1991).

Allergic reactions

Allergic reactions are a possibility, just as they are with many foods and pharmaceuticals. Those who have allergies, should look for contraindications in the research and consult with their healthcare providers. Day to day use vegetables such as cucumber,peanuts etc.can also be allergic to some

Improper dosage / usage

Adverse reactions may also result from inappropriate or improper usage, such as excess dosage. In these cases, the problem lies not with the botanical supplements, but with a failure of communication. Similar errors occur with pharmaceutical medicines as well, the solution in both cases includes proper education and effective communication.

Food/drug interactions

In practice, the most frequent adverse reactions to botanical medicines typically originate from interactions with prescription medicines, other dietary supplements, or in some cases, with foods. Jenetzky and Morreale (1997).

Brinker (1998) has identified the most potentially serious or life-threatening botanical/pharmaceutical interactions, wherein the botanical:

- Affects absorption of drugs
- Enhances potassium loss if given with diuretics
- Interacts with monoamine oxidase inhibitors
- Interacts with cardiac glycosides
- Enhances effects of barbiturates
- Alters effects of blood sugar medications
- Interacts with anticoagulant (blood thinning) medications.

Contamination & adulteration

Occasionally, supplements are contaminated with unwanted constituents, such as heavy metals, or even deliberately adulterated with pharmaceutical ingredients. Such failures in quality control are extremely rare, but when they do occur, they can be serious. These types of safety hazards are seen more frequently in herbal supplements imported from India, China, or other countries where quality control procedures are less stringent than in this country (Reports from University of Minnesota, 2007-2011).

CONCLUSIONS

The traditional medical systems are part of a time-tested culture and honored by people still today. For more than 3,000 years, these traditions have successfully set an example of natural resource use in curing many complex diseases. Many advantages of such eco-friendly traditions exist. The plants used for various therapies are readily available, easy to transport, and have a relatively long shelf life. The most important advantage of herbal medicine is the minimal side effects, and relatively low cost compared to the synthetic medicines. The success of medicinal plants sector mainly depends on the awareness and interest of the farmers as well as its other stakeholders, supportive government policies, availability of assured markets, profitable price levels, and assess to simple and appropriate agro-techniques.

The successful establishments of medicinal plants sector may help in raising rural employment, boost commerce around the world, and contribute to the health of millions .On the contrary, even the best drug becomes a potent poison if used incorrectly. A study by the European organisation of cosmetic ingredients, industries and services has found that some 27 toxic substances exist in the 350 plants used in the cosmetic ingredient, a result that consumers should be warned about, the reports finds. With consumers increasingly making the switch to natural and botanical-based products because they are believed to be safer, the need to communicate potentially dangerous toxins in such products is all the more pressing (Pitman, 2005). Euromonitor recently drew attention to research that shows that while the global market for cosmetic and toiletry products is expected to grow at just 1 per cent a year through to 2009, the market for natural-based cosmetic products, which includes botanicals, is expected to grow at 9 per cent per year between 2003 and 2009 to reach a value of $5.8 billion (Pitman, 2005).

To conclude, not all botanical/pharmaceutical interactions are harmful. For example, in some cases, botanicals can enhance the effect of a pharmaceuticals, thus allowing individuals to reduce their dosage Even a potent poison becomes the best drug on proper dosage administration.

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