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ADVERSE EFFECTS OF HERBAL MEDICINAL PLANTS – AN OVERVIEW

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Abstract

In the recent past years, although the use of herbal plant products and supplements has increased to a large extent, overall only less than 80% of people rely on them to provide some basic healthcare services. Despite the fact that treatments including these agents have shown promising potential with their efficacy, many of them remain experimental and their use is poorly monitored. As a result, this often led to inadequate information about their mechanism of action and lead to potential adverse reactions, contraindications and interactions with existing pharmaceutical drugs and functional foods. The use of herbal plant medicine and dietary supplements can be risky as they are not subject to review by the Federal Drug Administration. Therefore, safety of herbal plants continues to be a major issue with the use of herbal remedies, where it becomes necessary. Owing to the lack of information about medicinal plants, may results in mistaking plants that contain toxins. This review discusses toxicity-related issues and major adverse effects arising from the use of herbal medicinal products and also highlights some important challenges related to the misidentification of herbal plants.

Keywords: Herbal medicine; medicinal plants; adverse events; toxicity, nutraceuticals.

Introduction

Herbal medicines and nutraceuticals utilization continue to increase rapidly around the world with increasing number of people adopting these products for the treatment of various health challenges in different national health-care settings (WHO, 2004). Over the past year, an incredible rise in acceptance and public interest in natural treatment therapies has been witnessed both in developing and developed countries, with these herbal remedies being available not only in pharmacy as well as in food stores and grocery stores. It is assessed that up to 80% of the total population living in the developing world depend on herbal plants medicinal products as an essential source of healthcare and conventional practice which includes the utilization of herbs as an important part of their culture in those communities [1,2,3].

This is owing of the acknowledgement of the value of the natural medical system, particularly of Asian origin and the recognition of medicinal plants from ancient Pharmacopoeias that have appeared to have great healing power, in their natural form. This increase in the utilization of herbal plants makes safety issues regarding herbal medicines. Various types of herbal medicines are related to different plants and expose different issues. Problems in the quality of herbal medicines can be categorized into two main types: external

and internal. Complications and variance in ingredients of herbal medicines are internal problems. Complete and careful execution of Good Agricultural and Collection Practices (GACP) and Good Manufacturing Practices (GMP) could assuredly decrease the adverse events due to misidentification of herbal plants [4].

In this herbal medicine system, specifically, plants need an ethnomedical check of efficacy or safety. Sadly, there is no general administrative framework set up that ensures that any of these herbal plant medicines are safe. The reports on serious reactions are indicating the need for the development of effective marker systems for isolation and identification of the individual components. Standards for herbal drugs are being developed worldwide but as yet there is no common consensus as to how these should be adopted. Standardization, stability and quality control for herbal drugs are feasible, but difficult to accomplish. Further, the regulation of these drugs is not uniform across countries. There are variations in the methods used in different countries in achieving stability and quality control [5]

Botanical misidentification of plant material can play a role in toxic reactions in humans. Some plant descriptions in traditional Chinese medicine have changed over time, which may lead to unintended intoxication by using the wrong plants. The art of herbal medicine is to dissect pharmacologically and therapeutically valuable herbal drugs from harmful and toxic ones and to develop combinations of medicinal plants as safe and efficient herbal remedies. Standardization and strict control measures are necessary to monitor sustainable high-quality herbal products and to exclude contaminations that badly affect patients consuming herbal medicine [3], [4].

In contrast to single compound-containing allopathic medicinal products, herbal medicines usually contain a complex mixture of phytochemicals that are produced as secondary metabolites. Plant material can easily contain more than 150 ingredients, which makes identification of the causing factor for adverse effects and interactions difficult [6], [2].

Essentially, herbal remedies consist of portions of plants or unpurified plant extracts containing several constituents which are often generally believed to work together synergistically.

Table 1 Name of the herbal plants and adverse events caused by them.

No.	**Plant Name**	**Adverse effect**
1.	*Stephaniae sinica* Vernacular name: Anshu Ling Jin Bu Huan	Acute hepatitis
2.	*Larrea tridentata Vernacular* name: Chaparral	Hepatic failure Hepatorenal syndrome encephalopathy
3.	*Ephedra sinica* Vernacular name: Ma Huang	Tachycardia, difficulty in respiration, insomnia
4.	*Scutellaria baicalensis* Vernacular name: Chinese skull cup; Huang Qin	Acute drug-induced liver injury
5.	*Panax ginseng* Vernacular name: Renshen Yangrong Tang	Chronic renal failure
6.	*Vaccinium macrocarpon* Common name: Cranberry	Nephrolithiasis
7.	*Salix daphnoides* Vernacular name: Willow bark	Renal dysfunction
8.	*Pausinystalia johimbe* Vernacular name:	

	johimbe	Progressive renal failure and proteinuria
9.	*Aconitum napellus*	Ventricular arrhythmia
	Vernacular name: Aconite, monk's hood	
10.	*Tripterygium wilfordii* Hook F Vernacular name: Thunder god vine	Renal and cardiotoxicity
11.	*Cimicifuga racemosa* Vernacular name: Black cohosh	Acute hepatitis
12.	*Piper methysticum* Vernacular name: Kava kava	Acute liver failure
13.	*Valeriana officinalis* Vernacular name: Valerian	Liver toxicity, neurotoxicity

Toxicity Nephrotoxicity

Nephrotoxicity which starts mildly and temporarily but, if not detected earlier, could be severe with the elevated electrolytes in the blood such as potassium and magnesium. . There are two ways to detect nephrotoxicity. The first test is a simple test of blood urea nitrogen (BUN) and Second test is to check creatinine levels in blood together termed kidney function tests. Normal range values of BUN and creatinine are 10–25 mg/dl and 0.7–1.4 mg/dl, respectively.

The reason for nephrotoxicity after herbal medicine intake may be the addition of toxins during careless preparation, the addition of adulterants, heavy metals, and some pharmaceutical products intentionally to reduce cost or increase efficacy [7]. Herbs for example thunder god vine with botanical name *Tripterygium wilfordii* Hook that contain diterpenoid epoxide induces apoptosis causing kidney damage. Star fruit with botanical name *Averrhoa carambola* contains oxalate in high quantity, which can cause acute nephropathy. *Guaiacum officinale* L. (rough bark) and Arctostaphylos uva-ursi (cranberry) increase stone formation. *Aristolochia fangchi* causes well-known aristolochic acid nephropathy. *Callilepis laureola* DC (Impila) inhibits mitochondrial ATP synthesis. *Uncaria tomentosa* wild DC (Peruvian's Cat's Claw) causes acute allergic interstitial nephritis. Studies are being conducted on *Salix alba* L. (willow bark) analgesic nephropathy induction. *Ephedra sinica* Stapf (Chinese ephedra) affects the renin-angiotensin-aldosterone system. *Glycyrrhiza glabra* L. (Licorice) and *Harpagophytum procumbens* DC (devil's claw) inhibit renal transport processes [8].

Figure 1. Thunder God vine leaves, flower, dried powder

Hepatotoxicity

Hepatotoxicity, termed after two Greek words Hepar and Toxicon meaning liver and poison, respectively, may be defined as liver damage due to the chemical, drug, herb, or dietary supplement. The damage can be noticed by stomach pain, nausea, vomiting, change in urine and stool colour, jaundice, rash, frequent tiredness, weakness, fatigue, and fever. Laboratory tests include some liver function tests, which are conducted on blood samples for the detection of hepatotoxicity.

Hepatotoxicity caused by herbal medicine intake, mostly the incident rates are still to be reported. The severity of toxicity is widely variable between mild hepatitis to acute hepatic failure. The scoring system for allopathic medicines can be assessed but is not suitable for herbal medicines and needs validation. Many Ayurvedic and Chinese herbal medicines are reported to cause hepatotoxicity. Major hepatotoxic herbs are *Cimicifuga racemosa* (black cohosh), *Larrea tridentata* (chaparral), *Teucrium chamaedrys* (germander), *Scutellaria lateriflora* (American skullcap), and *Scutellaria baicalensis* (Chinese skullcap), etc [9].

Cardiotoxicity

Cardiotoxicity is a term used for damage to the heart or altering heart functions. It is a state in which there is an alteration in the electrophysiological function of the heart or cardiac muscle damage, which weakens the heart causing inefficient pumping and circulation of blood. This can be detected by symptoms such as dry, non-productive cough, inflammation of ankles, hand, feet, and neck veins; irregular heartbeat; tachycardia; cardiomegaly; weakness; vertigo, etc.

Herbal medicines having a direct effect on the heart include medicine prepared from plants such as *Digitalis purpurea* (digitalis), *Catharanthus roseus* (Vinca), *Aconitum napellus* (monk's hood), *Atropa belladonna* (deadly nightshade), *Ephedra distachya* (sea grape), *Mandragora officinarum* (mandrake), *Glycyrrhiza glabra* (licorice), etc [10].

Figure 2. Glycyrrhiza glabra leaves, flower, root and powder.

Neurotoxicity

Neurotoxicity is a term used for a state in which there is physical brain damage due to exposure to neurotoxin, a substance that disrupts or kills neurons, and in turn alters the activity of the nervous system. Signs and symptoms of this type of toxicity are anxiety, depression, limb weakness and numbness, impaired vision, headache, sexual dysfunction and behavioural changes.

Some common plants used as herbal medicines have potentially neurotoxic effects. Among them are *Papaver somniferum* (opium), *Catharanthus roseus* (Vinca), *Datura stramonium* (thorn apple), *Atropa belladonna* (deadly nightshade), *Hyoscyamus niger* (henbane), *Cannabis indica* (marijuana), *Conium maculatum* (hemlock), *Coscinium fenestratum* (yellow vine) [11], and Brugmansia species (angel's trumpet) [12].

Skin Toxicity

Cutaneous toxicity is a term used for an evident adverse effect such as skin irritation, inflammation, or rashes of epidermal growth factor receptors caused by exposure to a plant, chemical, or environmental factor. The most common source of skin toxicity is food and cosmetics, and others are medicated lotions, balms, creams, inhalers and essential oils. A variety of herbal material is available in all of the above-mentioned cosmetics and medicated products. Types of skin sensitization reactions include the following:

Primary Irritant Dermatitis:

It is a direct irritation of the skin with symptoms such as redness, itching, pain, blisters, peeling, or open wounds. Primary irritant dermatitis may be caused by plants such as *Cannabis sativa* (weed oil), *Dieffenbachia amoena* (dumb canes), *Asclepias syriaca* (milkweed), *Narcissus pseudonarcissus* (daffodils), *Digitalis purpurea* (foxglove), *Ricinus communis* (castor bean), *Tulipa gesneriana* (tulip bulb), *Primula veris* (cowslip), *Hevea brasiliensis* (rubber tree), *Ficus carica* (fig tree sap), *Ranunculus acris* (butter cup), etc. Common foods such as *Pastinaca sativa* (parsnip), *Solanum lycopersicum* (tomatoes), *Daucus carota* (carrot), *Cucumis sativus* (cucumber), *Brassica rapa* (turnip), *Petroselinum crispum* (parsley), *Apium graveolens* (celery) and *Agaricus bisporus* (mushrooms) also can cause primary irritant dermatitis.

Allergic Contact Dermatitis:

It is a true allergic response and is varied from individual to individual. *Toxicodendron diversilobum* (poison oak) and *Toxicodendron rydbergii* (poison ivy) are the most common plants producing allergic contact dermatitis. Others include *Hedera helix* (English ivy),

Toxicodendron vernix (poison sumac), *Dendranthema grandiflorum* (chrysanthemum), *Narcissus pseudonarcissus* (daffodils), *Tulipa gesneriana* (tulip bulb), Marchantiophyta species (liverwort), *Primula vulgaris* (prime rose), *Flavoparmelia caperata* (lichens), *Pinus sabiniana* (pine), *Cedrus deodara* (cedar), *Anacardium occidentale* (cashew), *Apium graveolens* (celery), *Allium cepa* (onions), and *Allium sativum* (garlic).

Photosensitization Dermatitis:

It is a cutaneous toxic response caused by exposure to sunlight when a photosensitizer (compound sensitive to sunlight) is present in the body and can be
detected by sunburn-like reactions in non-pigmented areas. Plants such as Tetradymia species (horse brushes), Hypericum species (St John's wort), *Tribulus terrestris* (goats head), *Agave lechuguilla* (Lechuguilla), *Bassia scoparia* (kochia), and *Lantana camara* (lantana) cause photosensitization dermatitis.

There is another type of phototoxic photosensitization caused by contact with some plants. When a photoactive chemical produced by plants comes in skin contact, absorbed and activated by sunlight, this type of reaction occurs. The intensity varies depending upon time and amount of exposure. Plants such as *Ficus carica* (figs), *Anethum graveolens* (dill), *Brassica alba* (mustard), *Petroselinum crispum* (parsley), *Citrus aurantifolia* (lime), *Daucus carota* (carrots), *Ranunculus acris* (butter cup), *Hypericum perforatum* (Klamath weed), and *Apium graveolens* (celery) with pink rot are reported to produce contact photosensitization [13].

Methodology

With the search through Elsevier, PubMed, Springer science and public media and Google Scholar for articles published between 2000 and 2021, using numerous keywords for example Herbal medicine; medicinal plants; pharmacognosy; adverse effects, toxicity, a total, of 15 articles were consulted for this study. [14] The objective of this study is to find out adverse events due to the misidentification of herbal plants. All the articles which discussed any related information and link were considered for this review.

Discussion

A single medicinal plant may contain hundreds of natural constituents and a mixed herbal medicinal product may contain several ingredients. Suppose every active ingredient were to be isolated from an individual herb from which the herbal medicine is formulated, the time and resources required would be tremendous. Such an analysis may practically be impossible especially where an herbal product is a mixture of two or more herbs [15].

Adverse events arising from the consumption of herbal medicines are attributable to several factors among which include the use of the wrong species of plant by mistake, adulteration of herbal products with other, undeclared medicines, contamination with toxic or hazardous substances, over dosage, misuse of herbal medicines by either healthcare providers or consumers and use of herbal medicines concomitantly with other medicines [16].

Furthermore, there is a lack of knowledge and/or poor emphasis on the importance of taxonomic botany and documentation by most manufacturers of herbal medicines and this poses peculiar challenges during the identification and collection of medicinal plants used for herbal remedies (Farah et al., 2000). To eliminate the confusion created by the common names, it is necessary to adopt the most commonly used binomial names (including their binomial synonyms) for medicinal plants such as *Artemisia absinthium* L. The herbal plant which contains an active narcotic derivative and is capable of causing CNS disorders and generalized mental deterioration, has at least 11 different common names seven of them does not match with its botanical name. *Heliotropium europaeum* (heliotrope), which contains

potent hepatotoxic pyrrolidine alkaloids, is often confused with Valerian Officinalis (garden heliotrope), known to contain valepotriates with sedative and muscle relaxant properties. [17] This explains why it is important to provide the exact scientific name of the plant, the plant part used and the name of the manufacturer when reporting adverse drug reactions of herbal medicines. Therefore, effective monitoring of the safety of herbal medicine will require effective collaboration between botanists, phytochemists, pharmacologists, and other major stakeholders.

Conclusion

The global acceptance and use of herbal medicines and related products continue to assume exponential increase. Issues relating to adverse reactions in recent times are also becoming more vivid, increasing in prevalence and no longer debatable because of the previous misconception regarding or categorizing herbal medicinal products as "safe" because they are derived from "natural" sources. The reality is that "safety" and "natural" are not synonymous. Therefore, regulatory policies on herbal medicines need to be standardized and strengthened on a global scale. Relevant regulatory authorities in different countries of the world need to be proactive and continue to put in place appropriate measures to protect public health by ensuring that all herbal medicines approved for sale are safe and of suitable quality.

Some herbal medicines have been used since ancient times for the effective treatment of disorders, and modern scientific scrutiny has confirmed the benefit of some herbal medicines based on pharmacological principles.

However, certain challenges make it difficult to obtain reliable data on herbal medicine safety such as misidentification [18] The education of healthcare professionals, providers of herbal medicines, and patients/consumers are vital for the prevention of potentially serious risks from misuse of herbal medicines.

Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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