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General Article

Phytotherapy–Safety aspects

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Abstract

Plants have been used since ancient times as medicines for the treatment of a range of diseases. In spite of the great advances observed in modern medicine in recent decades, plants still make an important contribution to health care. According to the World Health Organization (WHO), because of poverty and lack of access to modern medicine, about 65-80% of the world's population that are living in developing countries depend essentially on plants for primary health care. Phytotherapeutic agents are herbal preparations consisting of complex mixtures of one or more plants which contain active ingredients, plant parts or plant material in the crude or processed state. The data existing for most plants to guarantee their quality, efficacy and safety is insufficient. The concept that herbal drugs are safe and free from side effects is not always. Plants contain hundreds of constituents, some of which are very toxic namely the most cytotoxic anti-cancer plant-derived drugs is pyrrolizidine alkaloids, etc. However, the adverse effects of phytotherapeutic agents are less as compared with synthetic drugs. Several regulatory models for herbal medicines are currently available including prescription drugs, over-the-counter substances, traditional medicines and dietary supplements. Harmonization and improvement in the processes of regulation is needed for safety aspects related to phytotherapy.

Keywords: Herbs, Phytotherapy, Herbal safety, Toxic constituents.

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Introduction

Phytotherapeutic agents are normally marketed as standardized preparations in the form of liquid, solid, or viscous preparations and extracts. They are prepared by maceration, percolation or distillation (volatile oils). Solid or extracts are prepared by evaporation of the solvents used in the process of extraction of the raw material. Phytotherapeutic agents are often administered in a highly concentrated form so as to improve their therapeutic efficacy. However, some secondary metabolites present in the plants may produce undesirable side effects. The safety problems emerging with herbal medicinal products reflect a growing market, largely unregulated, where many of the safety concerns arise due to lack of effective quality controls. Other serious quality related safety problems include the deliberate addition of prescription medicines and toxic heavy metals to herbal products[1-3].

Increased usage and awareness of potential safety concerns have identified hitherto unknown safety problems associated with some traditional herbal products. Serious liver toxicity associated with the use of Kava-kava (***Piper methysticum* G. Forst.**) has been reported recently and it has been advised that the use of Kava-kava should be prohibited in unlicensed medicinal products. Other concerns, particularly interactions with conventional medicines, are the consequence of using conventional medicines and herbal products simultaneously and are of no surprise from a scientific viewpoint. Interactions, particularly those with medicines, can and do give rise to serious public health concerns. The potential for herb-drug interactions has been highlighted by the recognition that the widely used herbal remedy, St John's Wort (***Hypericum perforatum* Linn.**), may interact with certain important medicines. These include for example HIV protease inhibitors, oral contraceptives, cyclosporin and warfarin, leading to a loss or reduction in the therapeutic effect of these prescribed medicines[4,5].

Compared with well-defined synthetic drugs, herbal medicines exhibit some marked differences: The active principles of herbal drugs are frequently unknown so that standardization, stability and quality control, though feasible, may not be easy. Also the availability and quality of raw materials are frequently problematic and well-controlled double-blind clinical and toxicological studies to prove their efficacy and safety are rare. Though the occurrence of undesirable side effects seems to be less frequent with herbal medicines, well-controlled

randomized clinical trials have revealed that they may exist [6-8].

Therefore, there is an urgent need for the public to have an understanding of the risks posed by phytotherapy and to ensure that such products are used judiciously. This paper attempts to highlight the safety aspects that should be taken into consideration in phytotherapy. The safety concerns mainly fall into following five main categories:

1. Self-administration/ medication

Self-administration of any therapy in preference to conventional treatment may delay a patient seeking qualified advice, or cause a patient to abandon conventional treatment without first seeking appropriate advice. Toxicity due to herbal drugs can also be due to insufficient knowledge about the constituents and the dose of the drug. The safety of herbal medicinal products is of particular importance as most of these products are self-prescribed and are used to treat minor and often chronic conditions. Recent research highlights the fact that patients are reluctant to tell their doctors that they are taking herbal products and thus it is probable that adverse reactions to herbal products are under-reported[9,10].

The extensive traditional use of plants as medicines has enabled those medicines with acute and obvious signs of toxicity to be well recognized and their use avoided. However, the promise that traditional use of a plant for perhaps many hundreds of years establishes its safety does not necessarily hold true. The more subtle and chronic forms of toxicity, such as carcinogenicity, mutagenicity and hepatotoxicity, may well have been overlooked by previous generations and it is these types of toxicity that are of most concern when assessing the safety of herbal remedies[11,12].

Excessive ingestion: Excessive doses of Ginseng have been reported to cause agitation, insomnia and raised blood pressure and these have been referred to as abuse of the remedy. Side effects including mastalgia and vaginal bleeding have been reported for ginseng following the ingestion of recommended doses. Similarly excessive ingestion of Liquorice has resulted in typical corticosteroid-type side effects of oedema and hypertension[13,14].

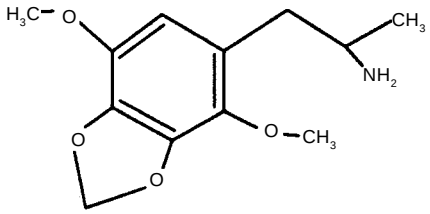
Hypersensitivity reactions: Sesquiterpene lactones are known to possess allergenic properties. They occur predominantly in herbs of the Asteraceae family and hypersensitivity reactions have been reported for Chamomile and other plants of this family. Cross-sensitivity to other members of this family is well recognized. The sesquiterpene lactones present in Feverfew are considered to be the active principles in the herb. It is unknown whether documented side effects for Feverfew, such as mouth ulcers and swollen tongue, are also attributable to this constituents[15].

Phototoxic reactions: Furanocoumarins, compounds known to cause phototoxic reactions, are constituents of Parsley [***Petroselinum crispum* (Mill.) Airy-Shaw**]. Excessive ingestion of Parsley has been associated with the development of photosensitive rash, which resolved once Parsley consumption ceased[16].

2. Intrinsically toxic phytoconstituents

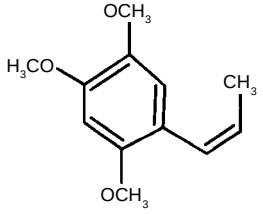
In many cases, the patient may be exposed to herbal ingredients which are potentially toxic and possess constituents that may cause adverse drug reactions. Very often the constituents responsible for toxicity are unknown (Table 1). Given below are some identified common examples of intrinsically toxic phytoconstituents.

Apiole: The irritant principle present in the volatile oil of parsley (***Petroselinum crispum***) is found responsible for its abortifacient action. Apiole is also hepatotoxic and liver damage has been documented as a result of excessive ingestion of parsley, far exceeding normal dietary consumption over a prolonged period[16].



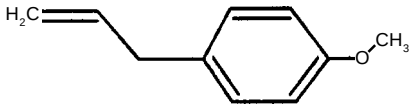
Apiole

β-Asarone: Calamus rhizome oil contains β-asarone as the major component, which has been shown to be carcinogenic in animal studies. Many other culinary herbs contain low levels of β-asarone in their volatile oils and therefore, the level of β-asarone permitted in foods as flavouring is restricted[16].



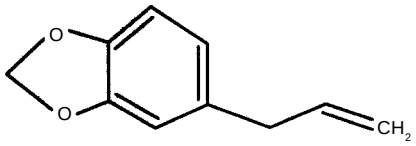
β-Asarone

Estragole: Estragole is a constituent of many culinary herbs but is a major component of the oils of Fennel and Sweet basil (***Ocimum basilicum* Linn.**). Estragole has been reported to be carcinogenic in animals and the level of estragole permitted in food products as flavouring is restricted[16].



Estragole

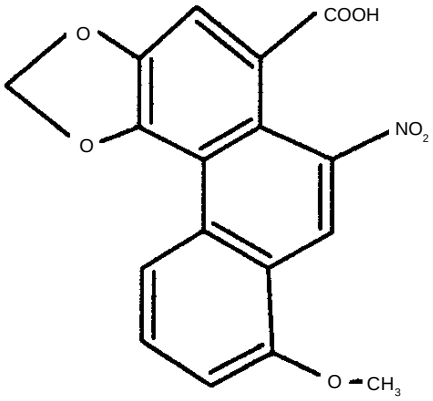
Safrole: Animal studies involving Safrole, the major component of Chinese sassafras oil [***Cinnamomum camphora* (Linn.) Nees & Eberm.**] have shown it to be hepatotoxic and carcinogenic. The permitted level of Safrole as a flavouring in foods is 0.1mg/kg[16].



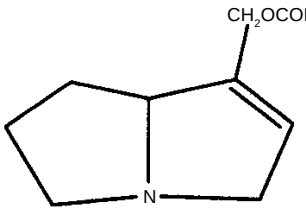
Safrole

Aristolochic acids: These are reported to occur only in the Aristolochiaceae family. They have been reported in ***Aristolochia*** species and appear to occur throughout the plant in the roots, stem, herb and fruit. The Aristolochic acids are a series of substituted nitrophenanthrene carboxylic acids. Aristolochic acids have been shown to be nephrotoxic, carcinogenic and mutagenic[17].

Pyrrolizidine alkaloids: These are present in a number of plant species, notably ***Crotalaria* Linn.** and ***Heliotropium* Linn.** These alkaloids are known to injure the liver in humans giving rise to serious liver damage (hepatic veno-occlusive disease). This hepatotoxicity associated with their consumption is well documented and has been attributed to the pyrrolizidine alkaloid constituents[18, 19]. Pyrrolizidine alkaloids can be divided into two categories based on their structure, namely those with an unsaturated nucleus (toxic) and those with a saturated nucleus (considered non-toxic). A number of herbs currently used in herbal remedies contain pyrrolizidines; they include Life root (***Senecio aureus* Linn.**), borage (***Borago officinalis* Linn.**) and Comfrey (***Symphytum officinale* Linn.**). In addition to various animal studies, two cases of human hepatotoxicity associated with the ingestion of comfrey have been documented. Following advice of the Committee on Review of Medicines (CRM), comfrey has been removed from all licensed products intended for internal use and is permitted only as an ingredient of products intended for external use on unbroken skin.



Aristolochic acid

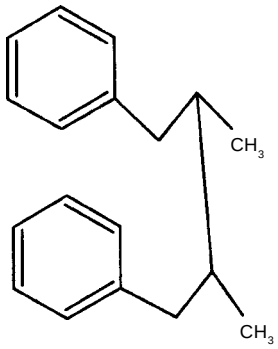


Basic nucleus of pyrrolizidine alkaloids

Lectins: Lectins are plant proteins which possess haemagglutinating and potent mitogenic properties. Both mistletoe (***Viscum album* Linn.**) and Pokeroot (***Phytolacca americana* Linn.**) contain lectins. Systemic exposure to Pokeroot has resulted in haematological aberrations. Mistletoe lectins may also inhibit protein synthesis[20].

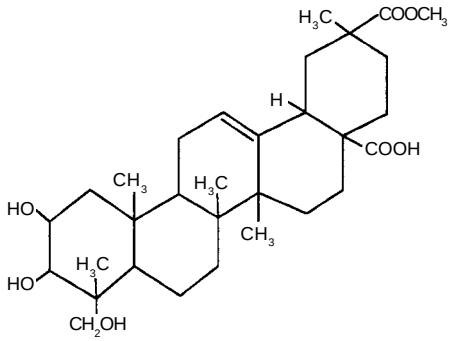
Viscotoxins: Viscotoxins are low molecular weight constituents of mistletoe (***V. album***), which possess cytotoxic and cardiotoxic properties. For many years, mistletoe preparations have been used in Europe for cancer treatment[20]. Clinical trials carried out with Iscador, a product obtained from the naturally fermented plant juice of Mistletoe, have concluded that Iscador may exhibit some weak antitumour effects but should only be used alongside conventional therapy in the long term treatment of cancer.

Lignans: The hepatotoxic reactions reported for Chaparral (***Larrea tridentata* J. M. Coult.**) have been associated with its lignan constituents[20].

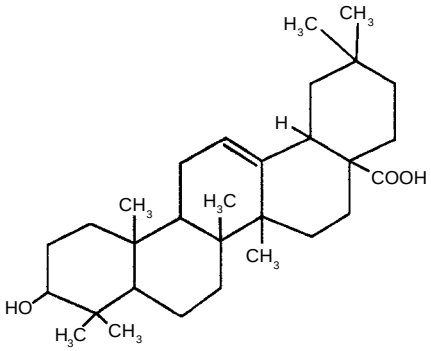


Basic lignan nucleus

Saponins: Pokeroot (***P. americana***) also contains irritant saponins which have produced severe gastrointestinal irritation involving intense abdominal cramping and haematemesis. Systemic exposure to these saponins has resulted in hypotension and tachycardia. In May 1979, the US Herb Trade Association requested that all its members should stop selling Pokeroot as a herbal beverage or food because of its toxicity. The saponins found in Pokeroot include phytolaccagenin and oleanolic acid[21].



Phytolaccagenin



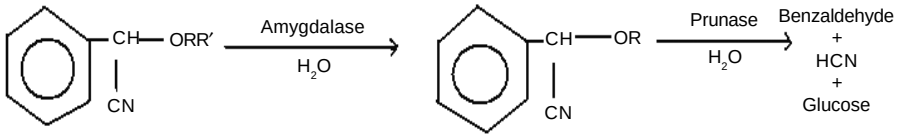
Oleanolic acid

Diterpenes: The irritant properties of many diterpenes are well documented. Queen's delight (***Stillingia sylvatica* Linn.**) contains diterpene esters which are extremely irritant to all mucosal surfaces.

Cyanogenic glycosides: These are present in the kernels of a number of fruits including Apricot, Bitter almond, Cherry, Pear and Plum seeds. Gastric hydrolysis of these compounds following oral ingestion results in the release of hydrogen cyanide (HCN), which is rapidly absorbed from the upper gastrointestinal tract and lead to respiratory failure. It has been estimated that oral doses of 50mg of HCN can be fatal, equivalent to about 50-60 Apricot kernels[22]. However, variation in cyanogenic glycoside content of the kernels could reduce or increase the number required for a fatal reaction. In the early 1980s a substance called amygdalin, a cyanogenic glycoside, was promoted as a natural non-toxic cure for cancer. Two near-fatal episodes of HCN poisoning have been recorded in which the patients had consumed Apricot kernels as an Alternative source of amygdalin[23].

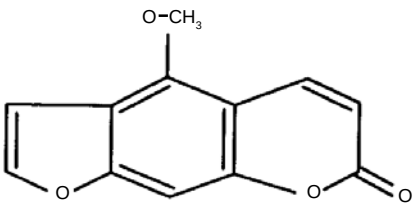
Furanocoumarins: These are found predominantly in the family — Apiaceae (Parsley, Celery), Rutaceae (eg. Bergamot, Citrus species), Moraceae and Fabaceae. The furanocoumarins occur as linear and branched forms. The most commonly reported linear furanocoumarins are 8-methoxypsoralen, 5-methoxypsoralen and psoralen itself. The furanocoumarins are phototoxic. Severe phototoxic reactions have been reported in humans following the use of Bergamot oil in topical preparations.

In UK a patient developed severe phototoxicity during oral photo-chemotherapy with psoralen and ultraviolet A (PUVA) therapy after eating a large quantity of soup made from Celery and Parsley[24-26].

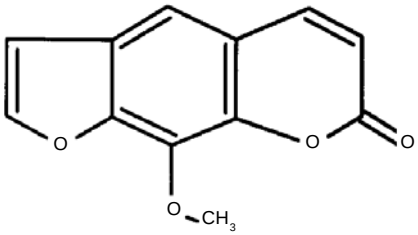


Amygdalin
(Where ORR'-genitiobiose)

Prunasin
(Where OR'-glucose)



5-Methoxypsoralen



8-Methoxypsoralen

Table 1 : Some potential toxic constituents of herbal medicines

Herbal drug	Adverse effect/toxicity	Toxic constituent
Aloe	Allergic reactions, headache, increase in menstrual flow	Anthraquinones
Arnica	Gastroenteritis, dermatitis	Anethole
Artichoke	Allergic contact dermatitis	Sesquiterpene lactones
Buchu	Gastrointestinal and renal irritation	Pulegone
Capsicum	Allergic alveolitis	Capsaicinoids
Dandelion	Contact allergic reactions	Quinones
Elder	Nausea, vomiting, diarrhoea	Cyanogenic glycosides
Garlic	Nausea, vomiting, diarrhoea, contact dermatitis	Sulphur containing compound
Ginkgo	Gastrointestinal upset, headache	Unknown
Ginseng	Hypertension, diarrhoea, insomnia, vaginal bleeding, skin eruption, nervousness	do-
Isapghula	Flatulence, abdominal distention, intestinal obstruction	do-
Liquorice	Hypertension, hypokelemia, weight gain	Glycyrrhizin
Lobelia	Nausea, vomiting diarrhoea	Lobeline
Rhubarb	Abdominal discomfort, loss of electrolytes, urine coloured red	Anthraquinones
Senna	Abdominal discomfort, loss of electrolytes, urine coloured red	Anthraquinones
St. John's wort	Allergic reactions	Unknown

3. Herb interactions

Herbal medicinal products may in some cases compromise the efficacy of conventional medicines, for example through herb-drug interactions, herb-herb interactions and herb-food interactions. A drug interaction is an interaction between a drug and another substance that prevents the drug from performing as expected. This definition applies to interactions of drugs with other drugs (drug-drug interactions), drugs with food (drug-food interactions) as well as drugs with other substances like herbs or vitamins. The interaction may increase or decrease the effectiveness and/or the side effects of the drugs. It may also result in a new side effect, that is, a side effect not seen with the use of any one drug alone[27].

The possibility of occurrence of a drug interaction increases with the number of drugs being taken by a patient. Therefore, individuals who take several medications are at the great risk for interactions. Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications[28, 29].

Herbal medicines are ubiquitous; the dearth of reports of adverse events and interactions probably reflects a combination of under-reporting and the benign nature of most herbs used. Experimental data in the field of herb-drug interactions are limited, case reports scarce and case series are also rare. This lack of data is also true of drug-drug interactions; published clinical studies are mainly case reports. Polypharmacy is common and to the mixture physicians prescribe, patients add various over-the-counter medications, vitamins, herbs and foods. All ingested substances have the potential to interact[29].

Pharmacodynamic types of herb-to-drug interactions are best identified by analyzing the therapeutic effect of the herbs and drugs (Table 2). Concurrent use of herbs and drugs with similar therapeutic actions will undoubtedly pose potential risk of herb-to-drug interactions. The increase in treatment effect interferes with optimal treatment outcome; the desired effect becomes more unpredictable and harder to obtain with precision. The highest risk of clinically-significant interactions occur between herbs and drugs that have sympathomimetic effects, cardiovascular effects, diuretic effects, anti-coagulant effects and anti-diabetic effects. Herbs with sympathomimetic effects may interfere with anti-hypertensive and anti-seizure drugs. The classic example of an herb with sympathomimetic effects is Ephedra, which contains ephedrine,

Table 2 : Herb-drug interactions[32]

Herb	Common uses	Interactions with	Problems which may occur
Ephedra	For asthma, cough and to induce weight loss	Cardiac glycosides, general anesthesia, MAO inhibitors, decongestants, stimulants	Seizures, adverse cardiovascular events, hypertension
Garlic	To decrease cholesterol and blood clot formation	Anticoagulants, Acetaminophen	Enhances bleeding, increase sulfation
Ginger	Nausea	Anticoagulants, barbiturates, antihypertensives, cardiac drugs, hypoglycemic drugs	Enhances bleeding, CNS depression, hypotension, cardiac arrhythmia, hypoglycemia
Ginseng	To increase energy and reduce stress	Anticoagulants, stimulants, antihypertensives, antidepressants/phenelzine, digoxin, potentiates the effects of corticosteroids and estrogens	Enhances bleeding, tachycardia and hypertension, mania, serotonin syndrome
Liquorice	Peptic ulcers and as expectorant	Antihypertensives, potentiates the effects of corticosteroids	Hypertension, hypokalemia, edema
St. John's Wort	Mild depression, anxiety, seasonal affective disorder	Anticoagulants, antidepressants, decreases the effectiveness of cyclosporine, antiviral drugs, digoxin, dextrometorphan, prolongs the effects of general anesthetics, MAO inhibitors, Nefazodone	Enhances bleeding, hastens metabolic breakdown of drugs, contra-indicated for organ transplant recipients, nausea, vomiting, headache

pseudoephedrine, norephedrine and other ephedrine alkaloids. Ephedra may interact with many other drugs and disease conditions and should always be used with caution in patients with hypertension, seizures, diabetes, thyroid conditions, etc. Concomitant use of diuretic herbs and diuretic drugs may have additive or synergistic effects; hypertension may be more difficult to control and/or hypotensive episodes may result. The dosage of herbs and/or drugs must be adjusted to achieve optimal treatment outcome. Commonly used diuretic herbs include ***Poria cocos*, *Polypori umbellata* Zhu ling** and ***Alismatis orientalis* (Sam.) Juzep**[30-32].

Herbs with anti-coagulant effects encompass herbs that have blood-activating and blood-stasis-removing functions. Such herbs may interfere with anti-coagulant drugs, such as warfarin, to prolong the bleeding time. Herbs that interfere with warfarin include ***Salviae miltiorrhizae* (Danshen)** and ***Angelica sinensis* (Oliv.) Diels**. The synergistic interaction between herbs and warfarin may be advantageous for the patient as the dosage of both the herbs and drugs can be reduced without compromising clinical effectiveness. The reduction in dosage will also decrease the frequency and severity of side effects of the drugs. Optimal treatment, however, is directly dependent on careful titration of the herb and drug, co-operation from the patient and communication between the physicians who prescribe the herbs and drugs[30,31].

Herb-food interaction and their risks have also been reported eg. Ginseng+ tea and coffee caused GIT upset and over stimulation[32] and consumption of St John's Wort and aged cheese causes fatal rise in blood pressure. Cuzzolin *et al*[33] have reported some serious reactions leading to hospitalization due to drug interaction (Table 3)

4. Quality related safety issues/Contaminants

The patient may be at risk of toxicity as a result of exposure to contaminants present in the herbal product (Table 4).

Substitution and adulteration: Herbal medicines adulterated with other plant materials and even with conventional medicines cause serious toxicity, e.g. Aristolochia was the most significant cause of plant toxicity in the last decade; inadvertent exposure to ***Aristolochia***

Table 3 : Serious adverse drug reaction leading to hospitalization due to drug interaction as reported by Cuzzolin *et al* [33]

Herbal product	Concomitant drug	Adverse drug reaction	Possible mechanism
Green tea	Contraceptives	Ischemia	Cardiovascular effects due to caffeine + increase in caffeine half life by hormones
Liquorice	-	Hypertensive crisis	Suppression of rennin-angiotensin-aldosterone axis by glycyrrhetinic acid
Liquorice	Contraceptives	Hypertensive crisis	Suppression of rennin-angiotensin-aldosterone axis by glycyrrhetinic acid+ increase in sensitivity to glycyrrhetinic acid by oestrogens
Passion flower	Benzodiazepines	Anaphylactic shock	Hypertensive reactions to the herb
Propolis	-	Systemic allergy	Hypertensive reactions to Propolis

Table 4 : Some adulterants and contaminants

Type of adulterant and contaminants	Examples
Botanicals (as adulterants)	Ailanthus and Phytolacca leaves substituted for Belladonna Xanthium leaves for Stramonium and Dandelion for Henbane
Microorganisms (as contaminant)	*Staphylococcus aureus, Escherichia coli, Salmonella, Shiegella*
Microbial toxins (as contaminant)	Aflatoxin, bacterial endotoxin
Fumigation agents (as contaminant)	Ethylene oxide, Methyl bromide, Phosphine
Toxic metals (as contaminant)	Lead, cadmium, mercury, arsenic
Pesticides (as contaminant)	DDT, chlorinated hydrocarbons, organophosphates, carbamates, polychlorinated biphenyls

species in unlicensed herbal medicines has resulted in cases of nephrotoxicity and carcinogenicity in Europe, China, Japan and USA. Concerns were first raised about the effects of products containing aristolochic acids in Belgium where since 1993 over 100 cases of irreversible nephropathy have been reported in young women attending a slimming clinic. The nephrotoxicity was traced to the inadvertent use of the toxic ***Aristolochia fangchi* Wu ex Chow & Hwang** root in the formulations as a substitute for ***Stephania tetrandra* Moore**. Other cases have been reported in China (seventeen cases with twelve fatalities) and Japan (ten cases of renal failure). Recently, the FDA has reported two cases of serious renal disease due to Aristolochia being substituted for ***Clematis*** species in a dietary supplement.

Microbial contamination: Aerobic bacteria and fungi are normally present in plant material and their number may increase due to faulty growth, harvesting, storage or processing. Herbal ingredients, particularly those with high starch content, may be prone to increased microbial growth. It is not uncommon for herbal ingredients to have aerobic bacteria present at 10^2-10^8 colony forming units per gram. Pathogenic organisms including *Enterobacter, Enterococcus, Clostridium, Pseudomonas, Shigella* and *Streptococcus* have been shown to contaminate herbal ingredients. The European Pharmacopoeia gives guidance on acceptable microbial limits[34].

Pesticides: Herbal ingredients, particularly those grown as cultivated crops, may be contaminated by DDT or other chlorinated hydrocarbons (Aldrin, Chlordane, Endrin, Benzene hexachloride, Heptachlor, etc.), organophosphates (Malathion, Parathion, Demeton, Ethion, etc.), carbamates (Zineb, Ziram, Thiram etc.) or polychlorinated biphenyls (2, 4-D, 2, 4, 5-T, etc.). Limit tests are necessary for acceptable levels of pesticide contamination of herbal ingredients[34].

Fumigants: Ethylene oxide, methyl bromide and phosphine have been used to control pests, which contaminate herbal ingredients. The use of ethylene oxide as a fumigant with herbal drugs is no longer permitted in Europe due to concerns about carcinogenic residues.

Toxic metals: Lead, cadmium, mercury, thallium and arsenic have been shown to be contaminants of some herbal ingredients. Limit tests for such toxic metals may be needed for certain herbal ingredients.

Other contaminants: Tests to limit other contaminants such as endotoxins, mycotoxins and radionuclides may need to be considered to ensure suitable quality for medicinal purposes[34].

5. Specific patient groups may be at risk

Pregnant/nursing mothers: Few conventional medicines have been established as safe to take during pregnancy and it is generally recognized that no medicine should be taken unless the benefit to the mother outweighs any possible risk to the foetus. This rule should also be applied to herbal medicinal products. However, herbal products are often promoted to the public as being natural and completely safe alternatives to conventional medicines[35]. Many herbs should not be used during pregnancy, or when nursing. These include Aloe, Angelica, Anise, Arnica, Ashwagandha, Cascara, Comfrey, Cubeb, Ephedra, Feverfew, Gymnema, Juniper, Lemongrass, Licorice, Lobelia, Myrrh, Parsley, Rhodiola, Sarsaparilla, Senna and Uva Ursi[36].

Many herbs are traditionally reputed to be abortifacient and for some this reputation can be attributed to their volatile oil component. A number of volatile oils are irritant to the genito-urinary tract if ingested and may induce uterine contractions. Herbs that contain irritant volatile oils include ground ivy, juniper, parsley, pennyroyal, sage, pansy and yarrow. Some of these oils contain the terpenoid constituent, thujone, which is known to be abortifacient. Pennyroyal oil also contains the hepatotoxic terpenoid constituent, pulegone. A case of liver failure in a woman who ingested pennyroyal oil as an abortifacient has been documented. A stimulant or spasmolytic action on uterine muscle has been documented for some herbal ingredients including Blue cohosh, Jamaica motherwort, Nettle and Raspberry. Some herbal teas contain laxative herbal ingredients such as senna and cascara. In general stimulant laxative preparations are not recommended during pregnancy and the use of unstandardized laxative preparations is particularly unsuitable[35, 36].

Pediatric use: Herbal remedies should be used with caution in children and medical advice should be sought if in doubt. Chamomile is a popular remedy used to treat teething pains in babies. However, Chamomile is known to contain allergenic sesquiterpene lactones and should therefore be used with caution. The administration of herbal teas to children needs to be considered carefully and professional advice may be needed[35].

Elderly: A recent review has considered the evidence available on the use of a number of herbal medicinal products by the elderly people. Whilst the treatments like St. John's Wort, Valerian, Ginkgo may offer considerable benefits for a range of conditions, there is need for caution when herbal medicinal products are used by the elderly particularly with regard to potential drug-herb interactions and possible side effects[37-39].

Conclusion

With the global increase in the use of traditional/complementary and alternative medicines in many parts of world, policy-makers, health professionals and the public are wrestling with questions about the safety, quality, availability, preservation and further development of this type of healthcare. Although herbs have promising potential and are being increasingly used, many of them are untested and their use is not monitored. As a result, knowledge of their potential side-effects is limited. This makes identification of the safest and most effective therapies and promotion of their rational use even more difficult. If phytotheraphy is to be promoted as a source of healthcare, efforts must be made to promote its rational use, and identification of the safest and most effective therapies will be crucial.

References

1. De Smet PAGM, The role of plant derived drugs and herbal medicines in healthcare, *Drugs*, 1997, **54**, 801-840.
2. Blumenthal M, Harvard study estimates consumers spend $5.1 billion on herbal products? *HerbalGram*, 1999, **45**, 68-74.
3. Blumenthal M, Herb industry sees mergers, acquisitions, and entry by pharmaceutical giants in 1998, *HerbalGram*, 1999, **45**, 67-68.
4. MCA Press Releases: Concern over Quality and Safety Standards of Traditional Chinese Medicines, September 2001.
5. MCA Notifications on Safety of Kava-kava products, December 2001-July 2002.

6. Grünwald J, The European phytomedicines market: figures, trends, analysis, *HerbalGram*, 1995, **34**, 60-65.

7. Roberts JE and Tyler VE, Tyler's Herbs of Choice, The Therapeutic Use of Phytomedicinals, The Haworth Press,Inc., New York, 1998.

8. Blumenthal M, Brusse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW and Rister RS, The Complete German Commission E Monographs, Therapeutic Guide to Herbal Medicines, The American Botanical Council, Austin, TX, USA, 1998.

9. De Smet PAGM, Health Risks of Herbal Remedies, *Drug Safety,* 1995, **13**(2), 81-93.

10. Barnes J, Mills SY, Abbot NC, Willoughby M, and Ernst E, Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies, *Brit J Clinic Pharmacol*, 1998, **45**, 496-500.

11. De Smet PAGM, Adverse Effects of Herbal Remedies, *Adv Drug React Bull*, 1997, **183**, 695-698.

12. Shaw D et al, Traditional remedies and food supplements, A 5-year toxicological study (1991-1995), *Drug Safety*, 1997, **17**, 342-56.

13. Baldwin CA, Anderson LA and Phillipson JD, What pharmacists should know about ginseng, *Pharm J,* 1986, **237**, 583-586.

14. D'Arcy PF, Adverse reactions and interactions with herbal medicines, Part 1. Adverse reactions, *Adverse Drug React Toxicol Rev,* 1991, **10**, 189-208.

15. Baldwin CA, Anderson LA and Phillipson JD, What pharmacists should know about feverfew, *Pharm J,* 1987, **239,** 237-238.

16. Tisserand R and Balacs T, Essential oil safety, Edinburgh: Churchill Livingstone, 1995.

17. De Smet PAGM, *Aristolochia* species in Adverse effects of herbal drugs, Vol.1, Berlin: Springer Verlag, 1992.

18. D'Arcy PF, Adverse reactions and interactions with herbal medicines, Part 1, *Adverse Drug React Toxicol Rev,* 1991, **10,** 189-208.

19. Mattocks AR, Chemistry and toxicology of pyrrolizidine alkaloids, New York: Academic Press, 1986.

20. Anderson LA, Phillipson JD, Mistletoe –The magic herb, *Pharm J,* 1982, **229**, 437-439.

21. Tyler VE, The Honest Herbal, 3rd Edn. New York: Howarth Press, 1993.

22. Chandler RF, Phillipson JD and Anderson LA, Controversial laetrile, *Pharm J,* 1984, **232,** 330-332.

23. Statutory Instrument (SI) 1984:87. The Medicines (Cyanogenetic Substances) Order, 1984.

24. Ljunggren B, Severe phototoxic burn following celery ingestion, *Arch Dermatol,* 1990, **126**, 1334-1336.

25. Boffa M J, Gilmour E and Ead R D, Celery soup causing severe phototoxicity during PUVA therapy, *Brit J Dermatol*, 1996, **135**, 330-345.

26. Medicines Control Agency, *Psoralea corylifolia* fruit in Traditional Chinese Medicines causing severe skin reaction, Current Problems, *Pharmacovigilance,* 2001, **27**, 12.

27. Ernst E, Possible interactions between synthetic and herbal medicinal products, *Perfusion,* 2000, **13**, 4-15.

28. Fugh-Berman A, Herb-drug interactions, *The Lancet,* 2000, **355,** 134-38.

29. Miller L, Selected clinical considerations focusing on known and potential drug-herb interactions, *Arch Inter Med*, 1998, **158**, 2200-2211.

30. Brown R, Potential interactrions of herbal medicines with antipsychotics, antidepressants and hypnotics, *Eur J Herb Med*, 1997, **3**(2), 25-28.

31. Boyle F, Herbal medicines can interfere with breast cancer treatment, *Med J Australia*, 1999, September 1st, 286.

32. European Pharmacopoeia, 4th edition, 2002, Strasbourg: Council of Europe, 2002.

33. Cuzzolin L *et al*, Safety implications regarding use of phytomedicine, *Eur J Clin Pharmacol,* 2006, **62,** 37-42.

34. Roulet M, Laurini R, Rivier L and Calame A, Hepatic veno-occlusive disease in newborn infant of a woman drinking herbal tea, *J Pediatr,* 1988, **112,** 433-436.

35. Allen JR *et al*, Are herbal teas safe for infants and children, *Austr Fam Physic*, 1989, **18**(8), 1017-19.

36. Ernst E, Herbal Medications for common ailments in the elderly, *Drugs and Ageing* 1999, **15**(6), 423-28.

37. Mashour NH, Herbal medicine for the treatment of cardiovascular disease, *Arch Intern Med,* 1998, **158**, 2225-2234.

38. Michael K. Ang-Lee; Jonathan Moss; Chun-Su Yuan, Herbal medicines and perioperative care, *J Amer Med Assoc*, 2001, **286**(2), 208-216.

39. Zhou SF, Zhou ZW, Li CG, Chen X, Yu X, Xue CC and Herington A, Identification of drugs that interact with herbs in drug development, *Drug Disc Today*, 2007, **12**, 664-673.