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Review Article

Impact of toxic heavy metals and pesticide residues in herbal products

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ABSTRACT

Medicinal plants have a long history of use in therapy throughout the world and still make an important part of traditional medicine. The World Health Organization (WHO) estimates that 65%–80% of the world's populations depend on the herbal products as their primary form of health care. This review is conducted to provide a general idea about chemical contaminants such as heavy metals and pesticide residues as major common contaminants of the herbal medicine, which impose serious health risks to human health. Additionally, we aim to provide different analytical methods for analysis of heavy metals and pesticide residues in the herbal medicine.

1. Introduction

1.1. Importance of herbal medicine

Greater attention has been paid to the herbal medicine even in developed countries. Herbal medicine has been used and trusted globally for thousands of years for their easy accessibility and restricted side effects (Padmavathi, 2013). Traditional medicines that are utilized by 80% of the population have compounds derived from herbal plants (Arunkumar and Muthuselvam, 2009). The medicinal values of these plants are usually due to the presence of phytochemical content as stated by Essien et al. (2012) and the most important of these phytochemicals include alkaloids, tannins, flavonoids and phenolic compounds.

The goals of using plants as sources of therapeutic agents include:

- Isolation of active principles for direct use as drugs, e.g., digoxin, digitoxin, morphine etc.
- Production of bioactive compounds of novel or known structures as lead compounds for production of patentable entities of higher activity and/or lower toxicity, e.g., oxycodone, taxotere, and verapamil, which are based, respectively, on morphine, taxol, and khellin.
- The usage of the agents as pharmacologic tools, e.g., lysergic acid diethylamide, mescaline, and yohimbine.
- The usage of the whole plant or part of it as a herbal remedy, e.g., peppermint oil, echinacea, garlic and *Ginkgo biloba* (Fabricant and Farnsworth, 2001).

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Table 1 – Examples for medicinal plants and their therapeutic uses.

Medicinal plants	Therapeutic uses
Garlic (*Allium sativum* L.)	Antiviral, antifungal, expectorant, anti-septic, anti-histamine (Hannan et al., 2011).
Artemisia (*Artemisia herba-alba*)	Antihelminthic and antimalaria drug (Mohamed et al., 2010).
Ginger (*Zingiber officinale*)	Act as analgesic, anti-inflammatory and hypoglycemic (Ojewole, 2006).
Ginkgo (*Ginkgo biloba* L.)	Antitussive (Mahadevan and Park, 2008)
Guava (*Psidium guajava*)	Potent anti-diarrheal, antihypertensive, hepatoprotective, hypoglycemic and antimutagenic activities (Nwinyi et al., 2008).
Eucalyptus (*Eucalyptus camaldulensis*)	Antibacterial, antifungal, analgesic and anti-inflammatory effects and antioxidative activities (Cheng et al., 2009).
Thyme (*Thymus vulgaris*)	Act as antispasmodic and anti oxidant, anthelmintic and has late been recommended as substitute as cancer prevention agent (Monira et al., 2012).

Medicinal plants are a source for a wide variety of natural antioxidants and are used for the treatment of diseases throughout the world (Rafieian-Kopaie and Baradaran, 2013). Medicinal plants, or their extracts, have been used in the prevention and treatment of several chronic diseases such as cardiovascular diseases, inflammatory diseases, arthritis, diabetes, and others as reported by Juhás et al. (2008).

The problems of high cost of synthetic drugs, residual effects on livestock products, adverse effects and development of drug resistance have led the researchers to find safe, potent, unconventional and economic natural drug sources as stated by Adedeji et al. (2008) (Table 1).

1.2. Sources of toxic chemicals in the medicinal herbal products

Medicinal plants may be easily contaminated by absorbing heavy metals from soil, water and air. Usually soil is subjected to contamination through atmospheric deposition of heavy metals from point sources including different industrial activities. Additional sources of these elements for plants are rainfall, atmospheric dusts and plant protection agents (Maobe et al., 2012).

Toxic elements from wastewater may contaminate agricultural soils, water supplies and environment and hence human food chain. The crops become contaminated and accumulate unfavorable levels of metallic elements within them. The up-take of metals by roots mainly depends on metal and soil characteristics and plant species etc. Thus, metal mobility in plants is very important to determine the effect of soil contamination on plant–metal uptake (Sobukola and Dairo, 2007).

Elevated levels of heavy metals in plants are reported from the areas having long-term uses of treated or untreated wastewater, plants growing along heavy traffic ways and previous dumpsites (Nwachukwu et al., 2010).

After collection and transformation of herbs into dosage form, the heavy metals confined in plants finally enter the human body and may disturb the normal functions of central nervous system, liver, lungs, heart, kidney and brain, leading to hypertension, abdominal pain, skin eruptions, intestinal ulcer and different types of cancers (Khan et al., 2008).

The storage and transportation conditions leading to the loss of the active ingredients, production of metabolites with no activity and the production of toxic metabolites play an important role in herbal contamination. Mites, nematode worms, insects, and beetles can also destroy herbal drugs during storage (Kunle et al., 2012).

Herbal drugs are accountable to contain pesticide remainders, which gather from agricultural practice, such as spraying, handling of soils during farming, and administering fumigants throughout storage (Kunle et al., 2012).

1.3. Effects of toxic chemicals on human health

1.3.1. Heavy metals

The term heavy metal refers to any metallic chemical element that has a relatively high density and is toxic at low concentrations. Metals are widely distributed throughout nature and occur freely in soil and water. Heavy metals in herbal preparations may not be a result of accidental contamination but may be introduced for supposed therapeutic properties; for example, mercury was used to treat syphilis until the introduction of penicillin, while arsenic-derived compounds are still used for treatment of some forms of malignancy.

Among the heavy metals mercury, lead, arsenic and cadmium are toxic metals and have mutagenic effects even at very low concentration. Several cases of human disease, malfunction and malformation of organs due to metal toxicity have been reported. Along with human beings, animals and plants are also affected by toxic levels of heavy metals (Sathiavelu et al., 2012).

The effects of toxicity vary between metals; for example, while lead poisoning typically may cause abdominal pain, vomiting, severe anemia, hemoglobulinuria and the stools have dark color owing to the presence of lead sulfide, mercury poisoning may cause peripheral neuropathy, psychological disturbances and arrhythmias may develop due to the toxic effect of mercury on the myocardium. Late, marked renal impairment occurs due to its nephrotoxic action leading to death.

The specific identification of metals is required for accurate diagnosis due to considerable overlap between the clinical syndromes associated with heavy metal poisoning (Ibrahim et al., 2006) (Table 2).

1.3.2. Pesticide residues

Pesticides are chemical compounds used to control or eradicate pests. According to their activity, they are grouped as insecticides, fungicides, nematocides, herbicides, rodenticides, and others (Britt, 2000).

According to chemical structure, they are grouped as organochlorine pesticides (OCPs) [hexachlorocyclohexanes (HCH),

Table 2 – Common uses, principal toxic effects and permissible limits of some heavy metals (Martin and Griswold, 2009; Singh et al., 2011).

Toxic metals	Industrial uses	Principal toxic effects	Permissible limits (mg/l)
Arsenic	Pesticides, herbicides	Lung cancer and skin diseases	0.02
Cadmium	Batteries, plastics, pigments, plating	Kidney damage, lung cancer and bone disorder	0.06
Chromium	Dyes , alloys, tanning	Respiratory effects, allergic dermatitis, kidney and liver damage	0.05
Lead	Batteries, wire and cable, alloys	Neurological effects, hematopoietic system damage and reproductive effects	0.1
Mercury	Chloro alkali industry, pesticides, thermometers, Batteries	Neurological effects and kidney damage	0.01
Manganese	Pesticides , batteries	Central nervous system effects	0.26
Zinc	Pharmaceuticals, dyes, Batteries	Gastrointestinal disturbances and anemia	15

dichlorodiphenylethanes (DDT)]; organophosphorus pesticides (OPs) [dichlorvos, malathion, and parathion]; nitrogen-containing pesticides (such as atrazin and propazin); pesticides of plant origin (pyrethroids and rotenoids), etc.

The residues of pesticides including their metabolites and/or degradation products will remain in plants, or in the soil that become a notable source of contamination for herbal medicines.

Currently pyrethroids pesticides detected both in domestic and imported herbal materials, such as *Panax notoginseng* root, and *Panax ginseng* root. These compounds are highly fat soluble, but are easily degraded and excreted in humans. Due to greater insecticidal activity and lower toxicity in mammals, pyrethroids are gradually replacing organochlorides and organophosphates as pesticides of choice (Britt, 2000).

Only OCPs (e.g. HCH) and a few OPs (e.g. carbophenothion) have long residual action (World Health Organization (WHO, 2007).

Organochlorines are central nervous system stimulants that can cause tremors, hyperexcitability and seizures. Although these pesticides are generally less acutely (immediately) toxic than organophosphates or carbamates, since they persist in the environment and tend to accumulate in tissue as they pass up the food chain, they are extremely hazardous. Organochlorine pesticide residues and breakdown products are found in human breast milk worldwide, and also in soil and plant and animal tissue from the middle of the Pacific Ocean to the Arctic Circle.

The main adverse effects associated with over exposure to OPs are symptoms of the nervous system; including headache, dizziness, paresthesia, tremor, discoordination, or convulsions. They inhibit the enzyme acetyl cholinesterase, which leads to the accumulation of acetylcholine in the nerve tissue and at the effectors organ, and to continued stimulation of cholinergic synapses. Delayed neuropathy is the main chronic effect of exposure to OPs (Britt, 2000) (Table 3).

2. Advances in chemical analytical and biomedical screening technology

2.1. *Chemical analytical systems*

2.1.1. *Flame atomic absorption spectrometry (FAAS)*

In atomic absorption spectrometry (AAS), light of a specific wavelength illuminates atoms in the ground state. The atoms may absorb the energy and as a result be elevated to an excited state.

The amount of light energy absorbed is proportional to the concentration of atoms present in the sample. A standard solution of known concentration of atoms can be used to establish the relationship, usually by performing a standard regression analysis.

A typical AAS consists of a primary light source, an atom source, a monochromator, a detector, and an electronic system to process the data, and a source uses a hollow cathode lamp or an electrodeless discharge display system to report the results. The light lamp: different lamps with different wavelengths are usually used to determine different elements accordingly. A multielement lamp can also be used to determine the concentration of more than one element without changing the lamp. In terms of detectors, solid-state detectors are being used recently to replace the use of photomultiplier tubes.

Flow injection mercury systems (FIMS) are atomic absorption spectrometers specialized to determine the concentration of mercury, which is a common source of contamination. FIMS use a high-performance single-beam optical system with a low-pressure mercury lamp and solar-blind detector to avoid interference and obtain optimal results. In order to analyze atoms, the atom source must produce free analyte atoms from the sample initially. One way to produce free atoms is to use heat generated by an air–acetylene or a nitrous oxide–acetylene flame. The sample can be introduced into the flame in a burner

Table 3 – Examples of limits (mg/kg) for some pesticide residues in medicinal plant materials (Ph. Eur., USP) (World Health Organization (WHO, 2007).

Substances	Ph. Eur. and USP
DDT	1.0
Diazinon	0.5
Malathion	1.0
Parathion	0.5
Dichlorvos	1.0
Fonofos	0.05
Dithiocarbamate	2.0
Alachlor	0.02
Aldrin and dieldrin (sum of)	0.05
Chlordane	0.05
Hexachlorocyclohexane isomers	0.3

head by a nebulizer in a spray chamber. In the mean time, the light beam passes through the flame and the light is absorbed according to the concentration of atoms.

Flame atomic absorption spectrometers have been used to determine concentrations of copper and manganese in herbal medicines (Dong and Zhu, 2003).

2.1.2. *Gas chromatography (GC) and volatile components in herbal medicines*

The analysis of volatile compounds by gas chromatography is very important in the analysis of herbal medicines. The GC analysis of the volatile oils has a number of advantages. First, the GC of the volatile oil gives a reasonable "fingerprint," which can be used to identify the plant. The composition and relative concentration of the organic compounds in the volatile oil are characteristic of the particular plant and the presence of impurities in the volatile oil can be readily detected. Second, the extraction of the volatile oil is relatively straightforward and can be standardized and the components can be readily identified using GC–MS analysis. The relative quantities of the components can be used to monitor or assess certain characteristics of the herbal medicines. Changes in composition of the volatile oil may also be used as indicators of oxidation, enzymatic changes or microbial fermentation. (World Health Organization (WHO, 2002a, 2002b)

2.1.3. *High performance liquid chromatography (HPLC)*

HPLC is commonly used to separate and analyze the concentration of molecules based on their polarity or lipophilicity. Heavy metals themselves cannot be determined by HPLC because, as ions, they lack the quality of lipophilicity. However, heavy metals can be complex with chelating agents during precolumn derivatization steps, whereupon the complexes can be separated and analyzed by reversed-phase high performance liquid chromatography (RP-HPLC). Therefore, the content of heavy metals can be determined by a UV detector operating at a certain wavelength, preferably providing maximum absorbance.

Porphyrins can chelate many metal ions to form 1:1 chelates, which are very stable and difficult to decompose under HPLC conditions. Based on this mechanism, a new method to measure heavy metals in Chinese herbal medicines was developed by microwave digestion and RP-HPLC.

After microwave digestion, lead, cadmium, mercury, nickel, copper, zinc and tin ions in the samples were mixed with tetra-(4-chlorophenyl)-porphyrin (T4-CPP) to form chelates. After extraction using a C18 cartridge eluted with THF, the chelates were separated using an RP18 column. Lead, cadmium, mercury, nickel, copper, zinc and tin contents in Chinese herbal medicine samples were measured by this method with good results (Yang et al., 2004). It was reported that heavy metal contents in the form of metal–organic complexes from the production of an anis-type beverage could be measured by HPLC. Several metals were found in the waste with concentrations of Fe at 157.5, Cu at 82.5, Zn at 31 and Ni at 8.5 mg/L (Moutsatsou et al., 2003).

2.1.4. *Gas chromatograph–mass spectrometry (GC–MS)*

Mass spectrometry is the most sensitive and useful method for molecular analysis and can give information on both the molecular weight and the arrangement of the molecule. Combine chromatography with mass spectrometry offer the advantage of both chromatography as a partition method and mass spectrometry as a detection system. In mass spectrometry first compounds allow to ionize and then divide the ions. Methods of ionization used in combination with gas chromatography are Electron Impact (EI) and Electron Capture Ionization (ECI).

Electron Impact (EI) is mainly directed to select positive ions, whereas ECI is usually directed for negative ions (ECNI). EI is mainly useful for regular analysis and provides reproducible mass spectra with structural information, which allows library searching. GC–MS was the first victorious online combination of chromatography with mass spectrometry and is widely used in the analysis of essential oil in herbal medicines (World Health Organization (WHO, 2002a, 2002b).

2.2. *Biomedical screening systems*

Problems related to chemical analysis have been identified that the level of the active components may be affected by physiological conditions, harvesting period and storage conditions, large amounts of samples are required for a proper analysis and some of the instruments such as HPLC; capillary electrophoresis and mass spectrometry are expensive and may not be available in many analytical laboratories.

Classical cytogenetic methods including chromosome counting and karyotyping may also be used to differentiate medicinal materials and play a role in assessing hybridity of plants (Magdalita et al., 1997).

One of the drawbacks of such markers is that the protein patterns vary in different tissues, developmental stages and environment as a consequence of temporal and spatial gene expression.

Distinguishable markers may also not be easily detected in closely related species and protein is prone to degradation after prolonged storage of the herbs.

DNA molecules are reliable markers for informative polymorphisms, as the genetic composition is unique for each individual and is less affected by age, physiological conditions as well as environmental factors. Additional advantages of DNA markers include: small amount of sample is sufficient for the analysis, which the physical form of the sample for assessment does not restrict detection. The DNA materials can be extracted from leaves, stems or roots of the herbal materials. Therefore DNA fingerprinting can be very useful to assess and confirm the species of the plant materials of interest. These techniques can be applied for the studies of other herbal medicinal materials using their crude extracts or bioactive fraction guided approaches.

3. Conclusion

The use of herbal products as the first choice in self-treatment of minor conditions continues to expand rapidly across the world. This makes the safety of herbal products an important public health issue.

Medicinal herbs should not be grown and/or collected in contaminated environments. Any chemicals used to boost growth or protect the crop should be kept to a minimum. Contamination with microbes, toxic elements and agrochemical residues after harvesting should be avoided as much as possible. Effective measures should be taken to prevent the spread of animals (insects and rodents) and microorganisms brought in with the herbal material to prevent cross-contamination.

It has been concluded from this study that estimation of heavy metals and pesticides is highly essential for raw drugs or plant parts used for the preparation of compound formulation drugs.

Further reading

Gogtay et al, 2002

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