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TOXIC HEAVY METALS FROM MEDICINAL HERBS-THE REASON YOU STILL FEEL SICK: AN OVERVIEW

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ABSTRACT

Drugs based on herbs have become a common form of therapy as well as for prophylaxis because they are often perceived as being natural and therefore harmless. Today they are one of the hottest trends and most sought after in the field of nutrition or herbal therapeutics. Plants experience oxidative stress upon exposure to heavy metals that leads to cellular damage. In addition, plants accumulate metal ions that disturb cellular ionic homeostasis. To minimize the detrimental effects of heavy metals exposure and their accumulation, plants have evolved detoxification mechanisms. Such mechanisms are mainly based on chelation and sub-cellular compartmentalization. Chelating of heavy metals is a ubiquitous detoxification strategy described in wide variety of plants. The article reviews the recent literature on heavy metal toxicity in herbal medicines, which imposes serious health risks to human health and reinforces the safety aspect of herbal products, which are considered to be relatively safe by common people.

KEYWORDS: heavy metals; metal toxicity; oxidative stress; free radicals, detoxification.

INTRODUCTION

Heavy metals include the transition-metal elements essential to plant nutrition, iron (Fe), zinc (Zn), manganese (Mn), copper (Cu), nickel (Ni) and molybdenum (Mo), cobalt (Co), which is required for nitrogen fixation in legumes, and the non-essential elements, chromium (Cr), cadmium (Cd), mercury (Hg) and lead (Pb).[1] According to World Health Organization (WHO) estimates, nearly 65–80% of the world population still primarily relies on nonconventional medications, mostly derived from herbal plants.[2,3] Herbal remedies are widely used for the treatment of various illnesses. They often contain highly active pharmacological components including minerals and trace metals.[4]

The metal distribution in the atmosphere is monitored by the properties of the given metal and by various environmental factors.[5] Heavy metals are generally referred to as those metals which possess a specific density of more than 5 g/cm3 and adversely affect the environment and living organisms.[6] These metals are quintessential to maintain various biochemical and physiological functions in living organisms when in very low concentrations; however they become noxious when they exceed certain threshold concentrations. Although it is acknowledged that heavy metals have many adverse health effects and last for a long period of time, heavy metal exposure continues and is increasing in many parts of the world. Heavy metals are significant environmental pollutants and their toxicity is a problem of increasing significance for ecological, evolutionary, nutritional and environmental reasons.[7,8] The most commonly found heavy metals in waste water include arsenic, cadmium, chromium, copper, lead, nickel, and zinc, all of which cause risks for human health and the environment.[9] Heavy metals enter the surroundings by natural means and through human activities. Various sources of heavy metals include soil erosion, natural weathering of the earth's crust, mining, industrial effluents, urban runoff, sewage discharge, insect or disease control agents applied to crops, and many others.[10] Figure 1 shows the global production and consumption of selected toxic metals during 1850–1990.[11] Although these metals have crucial biological functions in plants and animals, sometimes their chemical coordination and oxidation-reduction properties have given them an additional benefit so that they can escape control mechanisms such as homeostasis, transport, compartmentalization and binding to required cell constituents. These metals bind with protein sites which are not made for them by displacing original metals from their natural binding sites causing malfunctioning of cells and ultimately toxicity. Previous research has found that oxidative deterioration of biological macromolecules is primarily due to binding of heavy metals to the DNA and nuclear proteins.[12]

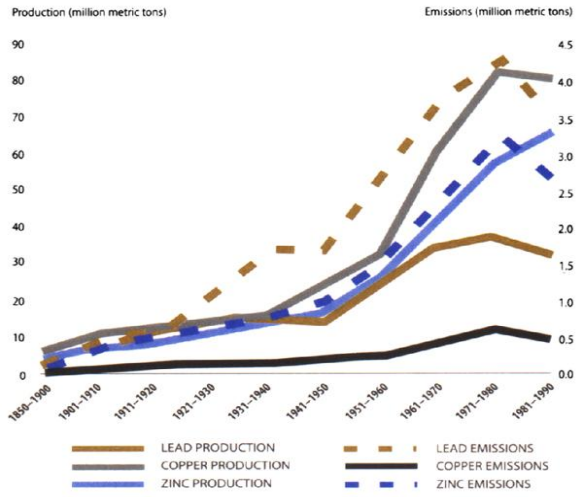

Fig 1.

Heavy metal impact on human health-A concise view

Heavy metals usually enter the human body via different food chains, medicinal herbs, inhalation, and ingestion. In addition, heavy metals have been used for long time by humans for making metal alloys and pigments for paints, cement, paper, rubber, and other materials. Even today the applications of heavy metals in some countries are increasing despite their well-known toxic effects. However, once the heavy metals enter the human body by any means, it is likely to stimulate the immune system and may cause nausea, anorexia, vomiting, gastrointestinal abnormalities, and dermatitis[13,14] The toxicity of heavy metals can also disrupt or damage the mental and central nervous systems[15], change blood composition[16], damage lungs[17], kidneys[18], livers[19], and other important organs.[20] The long-term exposures of human population to heavy metals have also shown physical, muscular, and neurological impairments. The degenerative processes are similar to Alzheimer's disease[17], Parkinson's disease[21], muscular dystrophy and multiple sclerosis.[22] Another disease such as obstructive lung disease has been linked to lung cancer, and damage to human's respiratory systems has also been found to develop following high rate exposure to metals. Apart from the toxic effects, certain metals like Cu, Se and Zn are reported to play some important and beneficial roles in human metabolism. As an example, Cu at lower concentration acts as co-factors for various enzymes of redox cycling[23,24]; however, at higher concentration disrupts the human metabolism leading to anaemia, liver and kidney damage, stomach and intestinal irritation.

Sources of toxic heavy metals in herbal medicines

The presence of heavy metals in herbal products is attributed to several possibilities. The environmental factors are probably contributed in the contamination of such products. It includes the contamination of the agricultural soils and irrigation water as a result of the industrial waste disposal, mining activities, preparation of the raw materials and the usage of certain types fertilizes.[25,26] The other possibility is the accidental contamination during the manufacturing process such as grinding, mixing and the exposure to heavy metals from metal releasing equipment which might be used in different steps of the processing part as shown in fig. 2.[27]

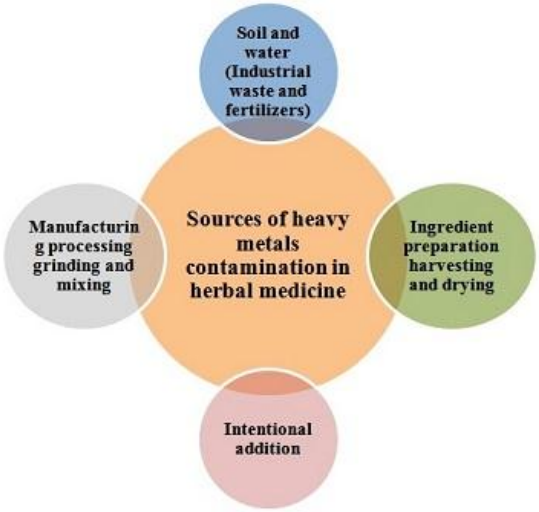

Fig 2: Sources of heavy metals contamination in herbal medicines.

Heavy metal–plant interactions

Exposure to heavy metals at higher concentrations results in severe damage to various metabolic activities leading consequently to the death of plants. The exposure of excess levels of metals to plants inhibits physiologically active enzymes[28], inactivates photosystems[29], and destruct mineral metabolism.[30] Sandmann and Boger[31] in a study have revealed the importance of lipid peroxidation under metal stress. Janas et al.[32] in other experiment have observed the impact of Cu on growth, lipid peroxidation, phenolic compound accumulation and localization in lentil (*Lens culinaris* Medic.) seedlings. Previous studies have reported that dissolved soil organic substances have significant effects on heavy metal transformations by increasing the solubility of heavy metal, root growth, and plant uptake.[33, 34] Recently published work demonstrated that maize and soybean grown in Cu and Pb contaminated soil had reduced photosynthetic pigments poor stomatal conductance, and significantly lower biomass.[35] On the other hand, Cd application resulted in a remarkable decline in the net rate of photosynthesis, stomatal conductance, and biomass in pakchoi and mustard plant.[36] In another study, Cd contamination resulted in increased total chlorophyll content in tomato and decreased total biomass.[37] Kuljeet Kaur et al. have shown that as a subsequent result of adding Zn and Cd individually into a hyper accumulator plant (*P. griffithii*), accumulation of both metals in roots, petioles, and leaves were significantly increased. However, Zn supplement influenced the Cd accumulation, in which it decreased Cd concentration in roots and increased the accumulation of Cd in petioles and leaves.[38] The protective effect of Mg against Cd toxicity could partially be due to the

maintenance of Fe status, the increase in anti-oxidative capacity, and protection of the photosynthetic apparatus.[39]

Heavy metal toxicity

Heavy metal poisoning is the accumulation of heavy metals, in toxic amounts, in the soft tissues of the body. Symptoms and physical findings associated with heavy metal poisoning vary according to the metal accumulated. Many of the heavy metals, such as**,** zinc, copper, chromium, iron and manganese, are essential to body function in very small amounts. But, if these metals accumulate in the body in concentrations sufficient to cause poisoning, then serious damage may occur. The heavy metals most commonly associated with poisoning of humans are arsenic, lead, mercury, and cadmium. Heavy metal poisoning may occur as a result of industrial exposure, air or water pollution, foods, herbal medicines, improperly coated food containers, or the ingestion of lead-based paints.[40] 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 as shown in Table 1.[41]

Table 1: Common uses, principal toxic effects and permissible limits of some heavy metals[42, 43]

Toxic heavy metals	Industrial uses	Principal toxic effect	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

Arsenic

Arsenic is one of the most important heavy metals causing disquiet from both ecological and individual health standpoints.[44] It has a semi-metallic property, is prominently toxic and carcinogenic, and is extensively available in the form of oxides or sulfides or as a salt of iron, sodium, calcium, copper, *etc*.[45] Arsenic is the twentieth most abundant element on earth and its inorganic forms such as arsenite and arsenate compounds are lethal to the environment and living creatures. Humans may encounter arsenic by natural means, industrial source, or from unintended sources. Drinking water may get contaminated by use of arsenical pesticides, natural mineral deposits or inappropriate disposal of arsenical chemicals.[46] Deliberate consumption of arsenic in case of suicidal attempts or accidental consumption by children may also result in cases of acute poisoning.[47, 48] Arsenic is a protoplastic poison since it affects primarily the sulphydryl group of cells causing malfunctioning of cell respiration, cell enzymes and mitosis.[49] Lower levels of arsenic exposure can cause nausea and vomiting, reduced production of erythrocytes and leukocytes, abnormal heart beat, pricking sensation in hands and legs, and damage to blood vessels. Long-term exposure can lead to the formation of skin lesions, internal cancers, neurological problems, pulmonary disease, peripheral vascular disease, hypertension and cardiovascular disease and diabetes mellitus.[50] Chronic arsenicosis results in many irreversible changes in the vital organs and the mortality rate is higher. In spite of the magnitude of this potentially lethal toxicity, there is no effective treatment for this disease.[51]

Mechanism of Arsenic toxicity

In arsenic biotransformation, harmful inorganic arsenic compounds get methylated by bacteria, algae, fungi and humans to give Monomethylarsonic acid (MMA) and Dimethylarsinic acid (DMA). In this biotransformation process, these inorganic arsenic species (iAs) are converted enzymetically to methylated arsenicals which are the end metabolites and the biomarker of chronic arsenic exposure.

iAs (V) →iAs (lll) →MMA (V) →MMA (lll) →DMA (V)

Biomethylation is a detoxification process and end products are methylated inorganic arsenic such as MMA (V) and DMA (V), which excreted through urine, are bio-indication of chronic arsenic exposure. However

MMA (III) is not excreted and remains inside the cell as an intermediate product. Monomethylarsonic acid (MMA III), an intermediate product, is found to be highly toxic compared to other arsenicals, potentially accountable for arsenic-induced carcinogenesis.[45, 52]

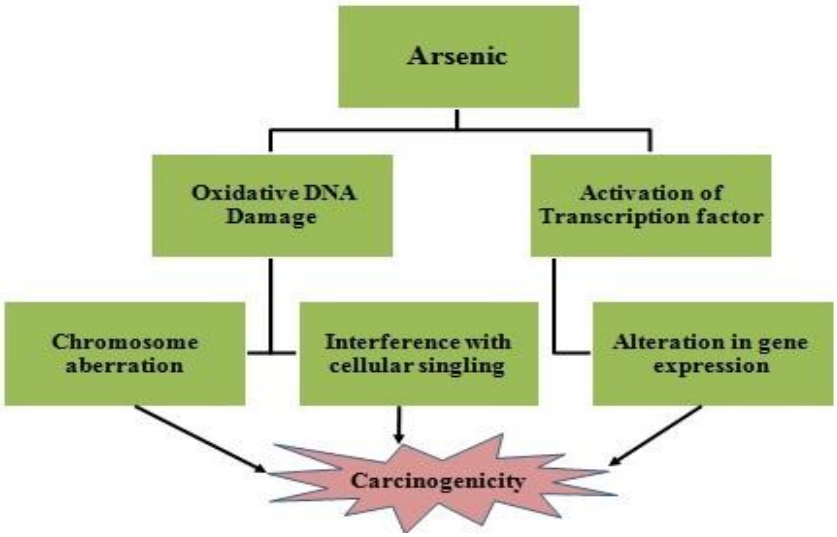

Fig 2.

Lead

Lead is one of the heavy metals which have been recognized for its undesirable effects on different body organs. Prolonged exposure to Pb decreases the performance of the nervous system and lowers renal clearance.[53] Lead poisoning is considered one of the significant environmental health threats for children even at low levels of exposure. It is associated with impairment of childhood cognitive function.[54] A high lead level during pregnancy is directly related to several outcomes such as spontaneous abortion, low birth weight and impaired neurodevelopment.[55] Lead poisoning occur when the concentration reach between 100-140 µg/L.[56] According to the international Agency for Research on cancer (IARC) inorganic lead is carcinogenic to human.[57] Figure 3 shows various sources of lead pollution in the environment.[58] The sources of lead exposure include mainly industrial processes, food and smoking, drinking water and domestic sources. Lead is an extremely toxic heavy metal that disturbs various plant physiological processes and unlike other metals, such as zinc, copper and manganese, it does not play any biological functions. A plant with high lead concentration fastens the production of reactive oxygen species (ROS), causing lipid membrane damage that ultimately leads to damage of chlorophyll and photosynthetic processes and suppresses the overall growth of the plant.[59]

Fig 3: Various sources of lead pollution in the environment.

Mechanism of lead toxicity

Lead metal causes toxicity in living cells by following ionic mechanism and that of oxidative stress. Many researchers have shown that oxidative stress in living cells is caused by the imbalance between the production of free radicals and the generation of antioxidants to detoxify the reactive intermediates or to repair the resulting damage. Figure 4 shows the attack of heavy metals on a cell and the balance between ROS production and the subsequent defense presented by antioxidants. Antioxidants, as *e.g.* glutathione, present in the cell protect it from free radicals such as H_2O_2. Under the influence of lead, however, the level of the ROS increases and the level of antioxidants decrease. Since glutathione exists both in reduced (GSH) and oxidized (GSSG) state, the reduced form of glutathione gives its reducing equivalents (H+ + e–) from its thiol groups of cystein to ROS in order to make them stable. In the presence of the enzyme glutathione peroxidase, reduced glutathione readily binds with another molecule of glutathione after donating the electron and forms glutathione disulfide (GSSG). The reduced form (GSH) of glutathione accounts for 90% of the total glutathione content and the oxidized form (GSSG) accounts for 10% under normal conditions. Yet under the condition of oxidative stress, the concentration of GSSG exceeds the concentration of GSH. Another biomarker for oxidative stress is lipid peroxidation, since the free radical collects electron from lipid molecules present inside the cell membrane, which eventually causes lipid peroxidation[60,61] At very high concentrations, ROS may cause structural damage to cells, proteins, nucleic acid, membranes and lipids, resulting in a stressed situation at cellular level.[62] The ionic mechanism of lead toxicity occurs mainly due to the ability of lead metal ions to replace other bivalent cations like Ca2+, Mg2+, Fe2+ and monovalent cations like Na+, which ultimately disturbs the biological metabolism of the cell. The ionic mechanism of lead toxicity causes significant changes in various biological processes such as cell adhesion, intra- and inter-cellular signaling, protein folding, maturation, apoptosis, ionic transportation, enzyme regulation, and release of neurotransmitters. Lead can substitute calcium even in picomolar concentration affecting protein kinase C, which regulates neural excitation and memory storage.[61]

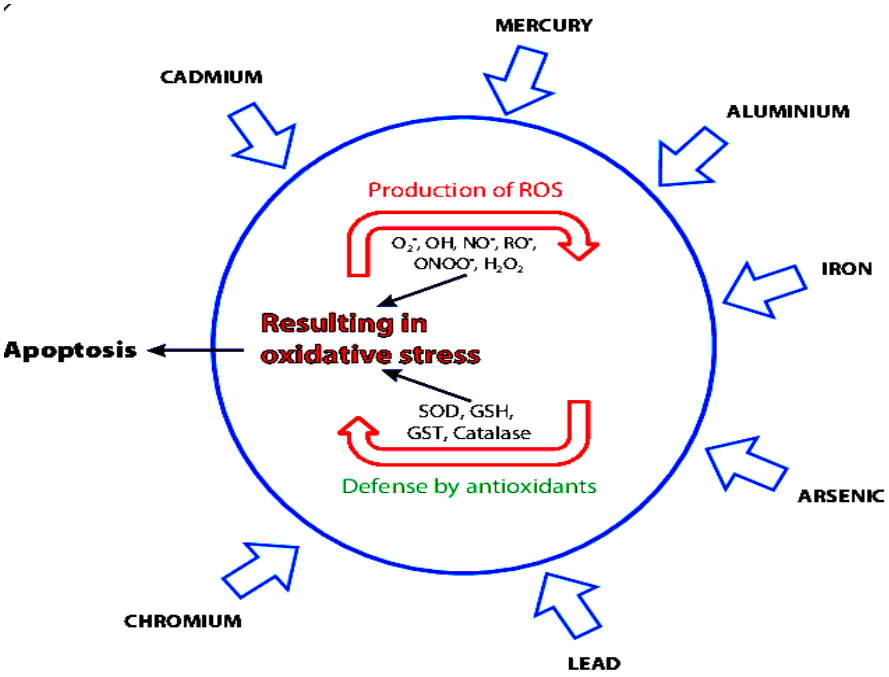

Fig 4: The attack of heavy metals on a cell and the balance between ROS production and the subsequent defense presented by antioxidants.

Toxicity of lead, also called lead poisoning, can be either acute or chronic. Acute exposure can cause loss of appetite, headache, hypertension, abdominal pain, renal dysfunction, fatigue, sleeplessness, arthritis, hallucinations and vertigo. Acute exposure mainly occurs in the place of work and in some manufacturing industries which make use of lead.

Chronic exposure of lead can result in mental retardation, birth defects, psychosis, autism, allergies, dyslexia, weight loss, hyperactivity, paralysis, muscular weakness, brain damage, kidney damage and may even cause death.[63] Figure 5 shows effects of increased lead level in blood.[64]

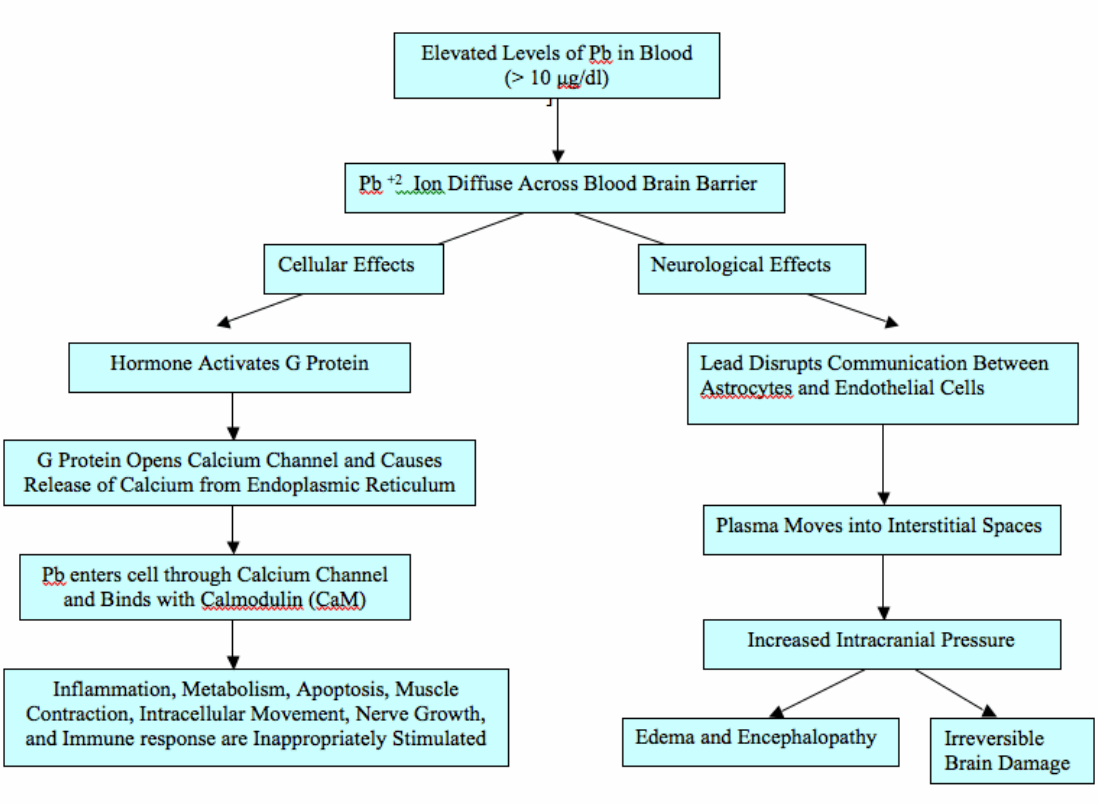

Figure 5: Effects of increased lead level in blood.

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. Current study is exposure to heavy metals can cause health hazard and toxicity. The presence of heavy metals in these medications could expose the consumers to different adverse health effects. Therefore, a proper general awareness should be provided to consumers and producers to minimize this risk.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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