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Review Article

USAGE OF HEAVY METALS IN AYURVEDIC FORMULATIONS AND ITS MANAGEMENT: A REVIEW

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ABSTRACT

Ayurveda is a comprehensive and systematic medicinal system, originated in India. It takes into consideration all aspects of health, including mental, physical and social components. According to the principles of Ayurvedic medication, heavy metals possess considerable therapeutic properties and can be administered to the patients after being processed properly as mentioned within the Rasashastra, in prescribed quantities. However, improper manufacturing processes might lead to higher levels of heavy metals remaining in the final product which may be dangerous. They may also be present as impurity rather than being added willfully. Heavy metals possess tendency to accumulate in vital organs and hence, pose a particular health risk. The presence of impurities in drug samples, whether herbal or pharmaceutical, is of great concern, not only because some contaminants are inherently toxic, but also they may negatively affect the stability of the drug and the lifespan, or they can cause unwanted side effects. The quality assurance of herbal formulations is the main concern of current phytomedical era due to the increase in toxicity reports. As a consequence, both organic and inorganic (elemental) impurities must be monitored and controlled in final dosage form starting from the raw materials itself. This article deals with the various aspects of heavy metals in Ayurvedic medicines such as their sources, methods used for their determination, their therapeutic significance, their toxic effects and also summarizes various guidelines and limits for their regulation.

KEYWORDS: Ayurvedic medicine, Heavy metals, Standardization, Significance, Toxicity, Permissible limits.

INTRODUCTION

The traditional Indian systems, which may also be called as Indian systems of Medicine (ISM), have a very solid conceptual basis and have been practiced continuously for a long time; therefore, they are considered as independent medical systems. Ayurveda, Siddha and Unani are the three important traditional systems practiced in India. Ayurveda is the oldest and most practiced system among the three with a consolidated history of many centuries. Ayurveda involves utilization of natural elements for elimination of root cause of the ailment by restoration of balance and creation of a healthy lifestyle in order to prevent its repetition.[1,2] The term Ayurveda is derived from two Sanskrit words in which AYU means life and VEDA means knowledge of. So, Ayurveda means having the 'knowledge of life'. According to Charaka, the ancient Ayurvedic scholar, "Ayu" or life consists of a combination of four essential parts: mind, body, soul, and senses. [3] Each of these must be nourished if an individual needs to have good health.[2] It is known that Ayurveda is a complete medical system that includes physical, psychological, philosophical, ethical and spiritual health and hence also is known as the "Mother of All Cures". [2,4]

In India there are more than 12,000 Ayurvedic universities and hospitals and clinics. According to the World Health Organization (WHO), about 70–80% of the world populations rely on nonconventional medicines mainly of herbal sources in their healthcare. [4,5]

The issues that require consideration includes-

- Development of National policy for the regulation of Ayurveda in India;
- Regulatory mechanism to control and regulate the production, use and certification of manufactured drugs in this sector, and
- Streamlining the facilities available for generating skilled labor, including clinical and paramedical staff, research and development aspects, and globalization of the system.
- Also strong emphasis is required to make ayurvedic medicines as the prescriptional

medicines rather than OTC products in order to make safe use and prevent harmful toxic and adverse effects of these drugs. [1,6]

Today, the world of medicine poses complex challenges. Therefore, time requires an integrated and pluralistic approach to medical care to effectively address this situation. To start fruitful dialogues between Ayurveda and modern science, a deep understanding of both systems becomes an essential prerequisite. [7]

Relevance of Ayurveda and Herbal Formulations

1. Herbal formulations are highly effective in a large number of diseases due to the presence of different phytoconstituents and the effects are further improved when compatible herbs are formulated together in the PHF (Poly-herbal Formulations).
2. It has been found that Poly-herbal formulations have a broad therapeutic range. Most of them are also effective at low doses and are safe at high doses, so they have a greater benefit ratio.
3. They produce fewer side effects than allopathic drugs. Although modern allopathic drugs are designed for effective therapeutic results, most of them have undesirable side effects such as insomnia, vomiting, fatigue, and so on.
4. Since PHFs are a product of nature, they are relatively cheaper, more environmentally friendly and readily available than allopathic medicines. Due to this, they are in demand around the world, especially in rural areas and in some developing countries, where expensive modern treatments are not available. [2]
5. They have better tolerance and patient acceptance.
6. Medicinal plants have a renewable source of cheaper medicines.
7. There are tremendous Improvements in the quality, effectiveness and safety of medicinal herbs with the development of science and technology.
8. They are more effective than any synthetic drug around the world. Herbal medicines have provided many of the most powerful medicines to the vast arsenal of medicines available for modern medical science, both raw and purely chemical, on which modern medicine is built. [8]

All the above reasons: effectiveness, safety, low cost, ubiquity, and better acceptance, have made Ayurvedic formulations an ideal treatment option, therefore providing greater patient compliance and an excellent therapeutic effect.[2]

Problems Associated With the Use of Herbal Formulations

1. There is a strong misconception that ayurvedic formulation is always safe, which is not true. CharakaSamhita has described that Ayurvedic medicines have adverse effects when prepared or used inappropriately.
2. Concomitant use of PHF with allopathic drugs has increased as most of the patients do not tell their doctors about concurrent treatments.
3. Clinical reproducibility of ayurvedic herbal formulation is difficult to obtain.
4. Ingredients of raw materials may vary depending on geographical location, climatic conditions, environmental hazards, collection methods and collection protocols, etc. So it is not easy to standardize the final product for a reproducible quality. This lot-to-lot variation would directly affect the effectiveness and safety of the PHF.
5. The need to modify the dosage regimen for the therapeutic effect needed also seems to be hectic as the dose needs to be calculated on the basis of whether crude drug or extract is used.
6. The toxicity of ayurvedic herbal formulas is prevalent but remains unresolved. It is well known that the presence of heavy metals in pharmaceuticals is not permitted, even in small quantities, to avoid toxicity. Drug experts estimate that around 6,000 drugs in the "Ayurvedic form" intentionally contain at least one metal, mercury and lead with the most commonly used. It is known that these toxic elements are potent nephrotoxic, hepatotoxic, neurotoxic and hematopoietic agents.
7. In India, considering that most ayurvedic PHFs are manufactured and exported, Ayurvedic herb preparation regulation is a bit less rigid, despite the establishment of the Drugs Act and the Cosmetic Act to control production control and quality. According to good clinical practice, toxicity studies and clinical studies on plant formulations are not mandatory for the application of patents and licenses to manufacture Ayurvedic herbal based products.[2,9]
8. Ayurvedic HMPs (Herbal Medicinal Products) are marketed as dietary supplements, they are regulated under the Dietary Supplement Health and Education Act (DSHEA), which does not require proof of safety or efficacy and hence bypasses the stringent quality tests of Drugs and Cosmetics Act 1940.
9. Generally cGMP are not given due consideration while manufacturing of Ayurvedic products hence it becomes necessary to continuously monitor the

processes in order to keep a check on adulteration and substitution.

10. Other considerations include toxic herbs, contamination with heavy metals, microbial organisms and pesticides as well as deliberate adulteration with pharmaceutical products. [10]

Regulations for Herbal Medicines

In addition to its use by more than 80% of the Indian population, Ayurvedic medicine and other traditional medicines from India are widely available all over the world.[6] Countries have their own set of laws and regulations for herbal as well as traditional medicines. WHO recommends that each country or area must adopt a regulatory system to manage the appropriate use of herbal medicine.[11]

In the United States, most herbal medicinal products from India are marketed as dietary supplements under the Dietary Supplement Health and Education Act of 1994. The Act does not require the submission of safety data or effectiveness for marketing approval. Manufacturers do not need to register their products with the United States Food and Drug Administration (FDA) or get approval before producing or selling food supplements. The FDA is responsible for taking action against potentially unsafe food supplements after it has hit the market.

However, in the European Union (EU), the request for authorization of traditional drugs to market requires bibliographic evidence and preclinical safety data (such as toxicological and pharmacological test data). According to the Traditional Medicinal Products Directive (2004/24 / EC), in order to obtain traditional registration for use, the applicant must submit quantitative and qualitative data on the components of the medicinal product, a description of the manufacturing methods, therapeutic indications, contraindications, adverse reaction, dosage, form and route of administration [Article 8 (3) (a) - (h), (j) and (k)]. The application also requires a summary of product characteristics without the clinical data specified in Article 11 (4) of Directive 2001/83/EC. In these circumstances, medicinal herbs will only be allowed if they can successfully overcome a complete regime requiring safety and efficacy data. It is likely to be very expensive for most medicinal herb manufacturers in India. [12]

In India, traditional herbal medicines, such as Ayurveda, Siddha and Unani (ASU), are considered safe due to its long history of use. As such, no safety and efficacy studies are required for marketing approval, according to the Drug and Cosmetics Act 1940 (DCA). IMCC (Indian Council Medical Center) Act, Research Tips (ICMR and CSIR), Department of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy) and the Drug Act and Cosmetic Act 1940 (Amendment) regulate medicinal herbs in India. [11]

When a publication in JAMA[13,14]posted warning about the toxic contents of some herbal-mineral preparations sold on US markets, the AYUSH Department took serious note of it. Administrative orders prescribing limits on the content of some of the minerals / metals were issued and directed the state governments and manufacturers to test each batch of ASU formulations for the metal content which have been intended for export.

In 2013, the then Department of AYUSH published the "Good Clinical Practice Guidelines for Clinical Trials in Ayurveda, Siddha and Unani Medicine" which will be followed by investigators, sponsors and drug manufacturers during clinical trials for ASU interventions.

The Ministry of AYUSH is also in the process of developing a Schedule Z for ASU drugs on the lines of Schedule Y of Drugs and Cosmetics Act for Biomedicine drugs. [15]

With the advent of the IPR regime, the department of AYUSH has also begun digitizing traditional medicinal formulations, manuscripts and knowledge and documentation, and promoting local health traditions. The Digital Library of Traditional Knowledge (TKDL) is a database containing codified literature of Indian medicine systems. It is a collaborative project between the Council of Scientific and Industrial Research (CSIR), the Ministry of Science and Technology and the Department of AYUSH, the Ministry of Health and Family Welfare, and is being implemented in CSIR.

Recently some regulatory guidelines have been introduced. The AYUSH Department and National Medicinal Plants Board (NMPB) has prepared India's Specific Guidelines on Good Agricultural Practices (GAPs). In the preparation of this standard, assistance has been taken from the Good Agricultural Practices and Field Collection Practices (GAFCPs) developed by the WHO in 2003 and Good Agricultural Practices set forth by the GLOBALGAP Secretariat which is implemented in more than 80 countries. [11]

Heavy Metals

The metals are widely distributed in nature and are found freely in soil and water. Heavy metals are metallic compounds of natural origin that have a high density compared to other metals, at least five times the density of water. [16]

Considering that heaviness and toxicity are inter-connected, heavy metals also include metalloids

such as arsenic, which can induce low-level toxicity. Heavy metals are also considered trace elements because of their presence in trace concentrations (ppb range to less than 10 ppm) in different environmental matrices.[17]

Any toxic metal can be called heavy metal, regardless of its atomic mass or density. [18] Any type of metal (or metalloid) can be considered a "contaminant" if it occurs where it is not desired, or in a form or concentration causing a harmful human or environmental effect. Metals/Metalloids include lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As), chromium (Cr), copper (Cu), selenium (Se), nickel (Ni), silver (Ag) and zinc (Zn). Other less common contaminants include aluminum (Al), cesium (Cs), cobalt (Co), manganese (Mn), Molybdenum (Mo), strontium (Sr) and uranium (U). [19]

Sources of toxic heavy metals in herbal medicinal products

Exposure to metals has increased dramatically over the last fifty years as a result of an exponential increase in the use of heavy metals in industrial processes and products. In developing countries, heavy metal pollution is exacerbated by mining, minerals, smelting and the tanning industry.

Heavy metal contamination is one of the problems that arise due to the increased use of fertilizers and other chemicals to meet the increased food production needs for human consumption and is one of the most pressing threats to water and soil, as well as to human health. [20]

The presence of heavy metals in herbal products is attributed to different possibilities.

- Environmental factors can contribute to the contamination of these products. It includes the contamination of agricultural soils and irrigation waters as a result of the elimination of industrial waste, mining activities and the use of certain types of fertilizers. [21]
- Natural sources of heavy metals such as the transport of volcano emissions from continental dust and the erosion of metal-enriched rocks due to the long exposure to air greatly increase the quantities of medicinal herbs in the soil.
- Furthermore, herbal medicines can also be contaminated by the soil through other human activities, such as: (i) the exploitation of mines and smelters (ii) the application of metal-based pesticides and sewage sludges enriched with metals in agriculture (iii)) combustion of fossil fuels, metallurgical and electronic industries, and (iv) military training and weapons, etc. [22]
- Toxic wastewater elements can contaminate agricultural land, water supply and the environment and thus the human food chain. The crops are contaminated and accumulate unfavorable levels of metallic elements inside them. [23]
- Heavy metals can also be introduced during the preparation of raw materials for herbal products that cover many steps, such as growing, harvesting, cleaning and drying medicinal plants.
- The other possibility is accidental contamination during the manufacturing process, such as grinding, mixing and exposure to heavy metals by metal release equipment that could be used at different stages of the processing part.
- Intentional addition of heavy metals during preparation as part of the healing ingredients is another source of heavy metal contamination.
- Heavy metals may also be leached into the drug substance and drug product from the container-closure systems. [21]

Analytical methods used for the quantitative determination of heavy metals

There are several approaches for the detailed analysis of heavy metals in environmental, biological and food samples. Analytical methods often require a pre-concentration of the sample and / or pretreatment for the destruction of the organic matrix such as wet digestion, dry ash and dissolution or extraction in a microwave oven. It is a huge challenge to develop sensitive and selective analytical methods capable of quantitatively characterizing trace levels of heavy metals in various types of samples.Table 1 summarizes the optical and electrochemical methods applied for the determination of heavy metals. [24]

Table 1: Most Usual Methods Applied for Determination of Heavy Metals[24]

Technique	Principle	Type of analysis	Applications
Atomic absorption spectrometry (AAS)	Absorption of radiant energy produced, by a special radiation source, by atoms in their electronic ground state	-Single element; -Multi-element analysis (2-6 elements)	Widely used
Inductively coupled plasma with atomic emission	Measures the optical emission from excited atoms	Simultaneous multi-element analysis	Widely used method for environmental analysis

spectrometry (ICP-AES)			
Inductively coupled plasma with mass spectrometry (ICP-MS)	- Argon plasma used as ion source; -Used for separating ions based on their mass-to charge ratio	Simultaneous multielement analysis	-Widely used; -Isotope determination
Atomic fluorescence spectrometry (AFS)	Measures the light that is reemitted after absorption	Single element	-Mercury, arsenic, and selenium; -Complementary technique to aas
X-ray fluorescence (XRF)	-X-rays -Primary excitation source; -Elements emit secondary X-rays of a characteristic wavelength	Simultaneous determination of most elements	-Non-destructive analysis; -Less suitable for analysis of minor and trace elements
Neutron activation analysis (NAA)	-Conversion of stable nuclei of atoms into radioactive ones; -measurement of the characteristic nuclear radiation emitted by the radioactive nuclei	Simultaneous multielement analysis	-Most elements can be determined; -Highly sensitive procedure
Electrochemical methods	-Controlled voltage or current; -Polarography; -Potentiometry; - Stripping voltammetry;	Consecutive analysis of different metal ions	-Analysis for transition metals and metalloids (total content or speciation analysis)

Heavy metal toxicity and metals of interest

Heavy metal toxicity is the accumulation of heavy metals in toxic quantities in the soft tissues of the body which starts affecting the normal functioning of the body. The symptoms and physical findings associated with heavy metal toxicity differ depending on the accumulated metal. Many of the heavy metals, such as zinc, copper, chromium, iron and manganese, are essential for the functioning of the body in very small quantities. But if these metals accumulate in the body in concentrations sufficient to cause toxicity, serious damage can occur. [25]

In ICH Guidelines, the elemental impurities have been sorted into different categories in order to facilitate decisions during the risk assessment. This classification has been summarized in Table -2 below:

Table2.Elemental Impurity Classfication [ICH Guidelines][26]

	Included Elemental Impurities	Include in Risk Assessment?	Description
Class 1	As, Pb, Cd, Hg	Yes	✓ Significantly toxic across all routes of administration. ✓ Typically have limited or no use in the manufacture of pharmaceuticals ✓ Can be present as impurities in commonly used materials (e.g., mined excipients). ✓ Cannot be readily removed from the material. Because of their unique nature, require consideration during the risk assessment.

Class 2	✓ Are toxic to a greater or lesser extent based on route of administration. ✓ Some of the elements in this category are infrequently observed as impurities in materials used to produce drug products and as such, unless intentionally added have a low probability of inclusion in the drug product and do not present a significant risk. ✓ Are further categorized to establish when they should be considered in the risk assessment and when their contribution can be judged to be negligible.		
Class 2A	V, Mo, Se, and Co	Yes	These require assessment across all potential sources and routes of administration due to their higher relative natural abundance (US Geological Survey, 2005).
Class 2B	Ag, Au, Tl, Pd, Pt, Ir, Os, Rh, and Ru	Yes only if intentionally added	These require assessment only if they are intentionally added to the processes used to generate the material under evaluation.
Class 3	Sb, Ba, Li, Cr, Cu, Sn, Ni	Dependent upon route of administration	✓ These are impurities with relatively low toxicity (high PDEs) by the oral route administration but require consideration in the risk assessment for other routes of administration (e.g., inhalation and parenteral routes). ✓ For oral routes of administration, unless intentionally added as part of the process generating the material, they do not need to be considered during the risk assessment. ✓ For parenteral and inhalation products, the potential for inclusion of these impurities should be evaluated during the risk assessment.
Class 4	B, Fe, Zn, K, Ca, Na, Mn, Mg, W, Al	No	✓ These are the impurities that have been evaluated but for which a PDE has not been established due to their low inherent toxicity and/or regional regulations. ✓ If these elemental impurities are present or included in the drug product they are addressed following the practices defined by other guidelines and regional regulation.

Since lead, arsenic, cadmium and mercury are considered as the most toxic heavy metals for human health; hence the discussion here is focused on these metals. Table 3 summarizes various aspects of heavy metals which are likely to contaminate ayurvedic formulations and are highly toxic even in small concentrations.

Important aspects of toxic heavy metals responsible for toxicity found present in Ayurvedic preparations [26-37]

Arsenic

Arsenic (As) is ubiquitous in the environment and present in food, soil, drinking water and in air and forms a variety of compounds, either inorganic or organic. Inorganic As occurs in trivalent (e.g., arsenic trioxide, sodium arsenite) or pentavalent forms (e.g., sodium arsenate, arsenic pentoxide, arsenic acid) which are generally known to be more toxic and are mainly of geological origin. Organic Arsenic compounds like Arsenobetaine, Arseno-choline, Arsenosugars and Tetramethylarsonium salts contain carbon and are mainly found in sea-living organisms. [38,39]

Source of exposure: Certain arsenicals are used as pesticides, fungicides and rodenticides, or used in glass, electroplating, dyestuff, paint and cosmetic industries as well as in semiconductor manufacturing. Coal-burning in power plants and smelters is the largest source of industrial arsenic.

Route of absorption: It includes Inhalation by lungs (arsine), Ingestion by GIT, and Absorption through skin.

Form of absorption: Inorganic salt or arsine gas

Distribution/targets: The distribution mainly depends on administration and type of arsenic compound involved. It is mainly stored in RBC (24 h), Liver, Kidneys, Lungs, Spleen, Muscles, CNS (4

weeks), Bone, Skin, Hair (an year), and can cross the placenta

Plasma $t_{1/2}$:

- Inorganic: ~10 h, 30 h, 200 h (tri-phasic)
- Organic: ~1 h

Excretion: The excretion is very slow and is mainly through urine and feces in man and may also bethrough sweat, milk and hair.

Toxicity mechanism: Arsenic (trivalent) binds to and inhibits SH-enzymes (sulfhydryl enzymes) by reacting with biological ligands having sulfhydryl groups.

Pharmacological action: It acts as an Antisyphilitic and antipyretic in certain febrile diseases. It is also helpful in treatment of certain skin diseases. Organic arsenicals are also used in the treatment of trypanosomiasis.

Therapeutic uses

Inorganic: It was used predominantly in leukemia, psoriasis, and chronic bronchial asthma in early times. Also beneficial in eczema and has antipyretic effect in certain febrile diseases.

Organic: Organic arsenic antibiotics were used extensively in the first half of the twentieth century, principally in the treatment of spirochetal and protozoal diseases and also in the treatment of syphilis.

Adverse reactions/ toxicity

Acute: Nausea, abdominal pain, laryngitis, bronchitis, vomiting and severe diarrhea. As fluid loss increases symptoms of shock appear. In severe poisoning death may occur in 1 h. If patient survives the acute episode, bone marrow suppression, encephalopathy and crippling sensory neuropathy may follow.

Chronic: It is usually due to inorganic arsenic and manifests as skin irritation and hair loss, sensory neuropathy, bone marrow depression, fatty liver, nephropathy, GIT irritation, etc.

Laboratory investigation: Arsenic can be measured in whole blood or urine, but the latter is to be preferred. The identification of stable non-toxic arsenic species, such as arsenobetaine, derived from dietary seafood is more difficult than measurement of total arsenic, but their presence can make the confirmation of arsenic poisoning from total arsenic measurements difficult.

Common Companion Testing: Fractionation or speciation.

Management of toxicity

Acute: Treatment consists of gastric lavage, i.v. fluids, correction of electrolyte balance and supportive care. In severe cases Dimercaprol 3-5 mg/kg i.m. every 4 h for 48 h is given.

Chronic: The intravascular volume is maintained. Dimercaprol is administered in a dose of 3 mg/kg i.m. every 4 h until abdominal symptoms subside. Penicillamine is substituted orally for Dimercaprol and continued for 4 days. The adverse effects of chelating agents limit the usefulness of the therapy. In severe arsenic-induced neuropathy dialysis is indicated.

Permissible limits [WHO]: 3 ppm

Cadmium

Cadmium (Cd) is a transition metal whose most abundant naturally-occurring isotope is non-radioactive. It is found in nature in mineral forms and is obtained for commercial uses principally from cadmium ore. Cadmium exists as a salt form in the +2 oxidation state only. Cadmium, cadmium oxide, cadmium salts on borosilicate carrier is used as catalysts in organic synthesis. Silver cadmium alloy is used in the selective hydrogenation of carbonyl compounds.

Source of exposure: Cadmium is often found near sites of metal mining and refining, production and application of phosphate fertilizers, waste incineration, and disposal. Occupational exposure is linked to battery, smelting, and electroplating industries. Also used in plastics and paint pigments. Cigarette smoking contributes to cadmium intake significantly.

Route of absorption: Absorption mainly occurs through lungs. It is poorly absorbed via- GIT and skin.

Distribution/targets: About 50 % of the total amount is deposited in Kidneys and Liver and is also stored in respiratory tract and bones.

Plasma $t_{1/2}$:1 month, 10–20 yrs (bi-phasic)

Excretion: The excretion is very slow and is mainly through feces. Urinary excretion becomes significant when there is significant renal damage.

Toxicity mechanism: Cadmium binds to cystein-rich low molecular weight protein such as metallothionein found in liver and kidneys. It also has the capability to bind with glutamate, histidine and aspartate ligands and can lead to the deficiency of iron.

Adverse reactions/ toxicity: Dyspnea, Emphysema, Pulmonary fibrosis, Glycosuria, Aminoaciduria, proteinuria, Hypertension, Itai-Itai disease (osteoporosis and osteomalacia).

Laboratory investigation: Both whole blood and urine concentrations are necessary for the assessment and monitoring of chronic cadmium exposure, as 90% of Cd is bound to erythrocytes and has a half-life of 70-120 days. The blood concentration depends on both current exposure and body burden and is generally a better guide to the

former than is urine Cd, unless the body burden is high. Urinary Cd excretion is positively correlated with cumulative exposure and with renal and hepatic concentrations

Common Companion Testing: Urine ß2-microglobulin

Management of toxicity: There is no effective therapy for Cd toxicity. Therapy with Calcium disodium EDTA (Ca Na_2 EDTA) 75 mg/kg per day in three to six divided doses is given for 5 days. The total dose should not exceed 500mg/kg per 5 day course.

Permissible limits (WHO): 0.3 ppm

Lead (*Naga*)

Lead (Pb) is the most common heavy element. It occurs in organic and inorganic forms. The generally bivalent Pb compounds include water-soluble salts such as Lead acetate as well as insoluble salts such as Lead oxides. Organic Pb compounds include the gasoline additives tetramethyl- and tetraethyl-lead. Organic Pb compounds undergo fairly rapid degradation in the atmosphere and form persistent inorganic Pb compounds in water and soil.

Source of exposure: Lead toxicity constitutes the oldest occupational disease in the world. Lead is widely used in industries e.g. in paints, battery, casings, illicit distillation, pipes, gasoline, etc. in addition, many lives in a lead-containing environment (air, food and water).

Route of absorption: Absorbed mainly through inhalation by lungs, ingestion by GIT and to some extent also from the skin.

Form of absorption: Metallic lead, inorganic or organic salts

Distribution/targets: After absorption lead is bound to RBC (24 h) and distributed to soft tissues (Liver, Kidneys, muscles, spleen, brain, bone marrow, etc.) and then to skin, hairs, nails and bones and can also crosses placenta.

Plasma $t_{1/2}$:30 days

Excretion: Excretion is very slow; and is primarily in stool; absorbed lead is excreted in urine, sweat and mother's milk.

Toxicity mechanism: Lead binds to –SH enzymes and forms complex ligands with many compounds and interferes with the activity of enzymes. It also interferes with actions of cations.

Pharmacological action: It acts as an Appetizer, aphrodisiac, and an immunomodulator. It alleviates urinary tract disorders and diseases caused by vitiated *Vata* and *Kapha*.

Therapeutic uses: *Naga bhasma* is indicated in Diabetes, rheumatoid arthritis, tetani, fever, anemia, dyspnea, cough, emaciation, cachexia, oedema, abdominal tumor, bowel syndrome, piles, ulcer, diarrhea, etc. it is also prescribed in all water borne diseases.

Therapeutic dose: 1/4th to1 Ratti (30 to 125 mg)/ day.

Adverse reactions/ toxicity

Acute: Not so common. Manifestations include thirst, metallic taste, nausea, vomiting and abdominal pain, paresthesias, muscle weakness, haemoglobinuria, oliguria and kidney damage.

Chronic: It affects gastrointestinal, CNS, hematopoietic system, kidney and others. The system may be affected alone or in combination. CNS is affected commonly in children, while the gastrointestinal system is affected in adults.

Laboratory investigation: The 'gold standard' for estimating the internal dose of lead has been measurement of its excretion after the administration of 1g of calcium ethylenediaminetetra-acetic acid (EDTA) (as an i.v. infusion or i.m. injection). Excretion during the next 24 h of more than 3·9/µmol (800/µg) lead in adults, or 2.9-3.4/µmol (600- 700/µg) in children, indicates a raised body burden.

Common Companion Testing: Blood zinc protoporphyrin (ZPP), CBC, *∂*-amino levulinic acid

Management of toxicity

In Ayurveda: *Hema* (gold) and Powder of *Terminalia chebula* (*Haritaki*) should be given repeatedly along with sugar candy (*Sita*) for 3 days.

In Allopathy

In acute phase supportive measures are given. Fluid and electrolyte balance must be maintained. Edetate calcium disodium and Dimercaprol are used together usually. Former is given in dose of 50-75 mg/kg/day in 2 divided doses by i.v. or i.m. injection.
Dimercaprol is given at a dose of 4 mg/kg every 4 h for 48 h the every 6 h for 48 h and every 6-12 h for additional 7 days

Permissible limits (WHO): 10 ppm

Mercury (*Parada*)

Mercury (Hg) is an element widely existing in the global environment. Hg exists in three forms: elemental mercury, inorganic mercury and organic mercury. Mercury is the only metal which is liquid under ordinary conditions. The most likely form of residual mercury in drug products is the inorganic form. Methyl mercury, the common, poisonous form, occurs by methylation in aquatic biota or sediments (both freshwater and ocean sediments).

Source of exposure: Mercury is used in: dental amalgams (50% by weight), explosive detonators; some vaccines in pure liquid form for thermometers,

barometers, and laboratory equipment; batteries and electrodes ("calomel"); and in fungicides and pesticides and in the paper industry. Emissions from coal fired power plants and hospital/municipal incinerators are significant sources of Mercury pollution.

Route of absorption: Absorption is dependent on the chemical form of mercury. Absorption of elemental mercury is poor but it can be absorbed from lungs. Occupational poisoning is mainly due to inhalation by Lungs (elemental Hg). Other routes include ingestion by GIT and Absorption through skin.

Form of absorption: Metal, Inorganic salt (Hg^{+2}), Organic (short chain).

Distribution/targets: After absorption highest concentration of mercury occurs in renal tubules. Other targets are CNS, Blood and GIT.

Plasma $t_{1/2}$:

- **Inorganic:** 3 days, 20 days (bi-phasic)
- **Methyl mercury:** 52 days

Excretion: Excretion is slow and chiefly through urine although some is removed through sweat and gastrointestinal tract.

Toxicity mechanism: Hg+2binds to SH-enzymes and gets concentrated in kidneys and CNS.

Pharmacological action: It is used in a compound (Murchita) form. It possesses aphrodisiac and anti-ageing properties. These increase potentiality, intellect, memory, attentiveness, and complexion and tissue elements. These eradicate diseases caused by all the three humoral principles even restricting death.

Therapeutic uses: Mercurial preparations are used in anemia, dyspnea, cough, jaundice, fever, spasmodic pain, nephritis, vomiting, acute abdomen, worm infestation, diarrhea etc.

Therapeutic dose: 1 *Ratti* (125 mg)/ day

Adverse reactions/toxicity: The improperly prepared mercurial preparations may cause various ill effects.

Acute: Shock, gingivitis, nausea, vomiting, gastroenteritis, renal failure and liver damage.

Chronic: Skin disorders, osteoarthritis, stomatitis, increased salivation, anorexia, anemia, hypertension, multiple neurological disorders and even death.

Laboratory investigation: The diagnosis of mercury poisoning is based on demonstrating concentrations higher than the limits for either whole blood or urine (early morning or 24 h collection). Urine is however easier to measure. It is analytically possible to measure total and inorganic mercury separately in blood or urine. Urinary mercury reflects exposure during the previous 2-3 months; blood mercury with its shorter half-life reflects exposure in the preceding week.

Management of toxicity

In Ayurveda

Sulphur is mentioned as a specific drug, other remedies are also described like *Dhanyaka* (*Coriandrum sativum*) with sugar candy or *Marich* (*Piper nigrum*) with ghee (clarified butter) should be given repeatedly for 7 days.

In Allopathy

Acute: Dimercaprol is given in dosage of 3-5 mg/kg i.m. every hour for 48 h and then every 12 h for 10 days.

Chronic: Oral penicillamine or N-acetylpenicillamine (250-500 mg orally) four times daily for 10 days.

Permissible limits [WHO]: 1 ppm

Therapeutic significance of heavy metals

Heavy metals in herbal preparations may not only be the result of accidental contamination but may be introduced for presumed therapeutic properties; For example, mercury has been used to treat syphilis until the introduction of penicillin, while arsenic derived compounds are still used to treat some forms of malignancy. [31]Although the biological effects of various metals are well known, little is known about their biological activity in terms of elemental properties. [27]

During the middle ages, with the advent of Rasashastra, the use of some heavy metals and minerals increased in ayurvedic therapies. Rasashastra is an integral part of Ayurveda which deals with drugs of mineral origin and details their varieties, characteristics, processing techniques, properties, therapeutic uses, the ability to develop adverse effects and their manipulation, etc. in an integral way. [28]

The metals used in the Ayurvedic medicine system include mercury (Parada), gold (Swarna), silver (Rajata), copper (Tamra), iron (Lauha), tin (Vanga), lead (Naga), zinc (Yasada) etc. Metal Bhasmas are the result of a series of physico-chemical processes. These are considered easily absorbable in humans and produce an optimal benefit at a minimum dose. [27]

Table 3: Important Aspects of Some Important Heavy Metals Used in Ayurvedic Formulations to Treat Various Ailments [27]

Heavy metals	Pharmacological actions	Therapeutic indications	Therapeutic dose	Adverse effects/Toxicity	Management of toxicity
Gold (Swarna)	Aphrodisiac, cardiac stimulant, immuno-modulator, increases potentiality, complexion, longevity, intellect, memory and attentiveness, in management of poisoning. It alleviates disorders caused by all the three vitiated *Doshas*.	Tuberculosis, schizophrenia, fever, grief, anemia, dyspnea, cough, worm infestation, anorexia, ophthalmic disorders and in poisoning.	1/8th to 1/4th *Ratti* (15 to30 mg)/ day	Weakness, impotency, leads to imbalance of homeostasis and even death.	Powder of *Terminalia chebula* fruit should be given repeatedly along with sugar candy (*Sita*) for 3 days.
Silver (Rajata)	Aphrodisiac, anti-ageing, scraping, immunomodulator properties, increases potentiality and intellect. It eradicates diseases caused by all three vitiated *Doshas*.	Diabetes, vitiligo, tuberculosis, anemia, dyspnea, cough, ophthalmic disorders, piles, thirst, emaciation and in poisoning.	1/4th to 1 *Ratti* (30 to125 mg)/ day.	Anemia, itching, fever, constipation, cervical lymphadenopathy, oligospermia, weakness, headache and reduce potency.	Sugar and honey should be given repeatedly for 3 days.
Copper (Tamra)	Rejuvenator, wound healer, emaciator, purgative and immunomodulator. It alleviates disorders caused by *Kapha* and *Pitta*.	Fever, anemia, dyspnea, cough, worm infestation, emaciation, anorexia, dyspepsia, abdominal tumor, splenic disorder, liver disorder, fainting, spasmodic pain, peptic ulcer, ascitis, diabetes, bowel syndrome, piles, rhinorrhea, acidity, etc.	1/8th to ½ *Ratti* (15 - 60 mg)/ day.	Vomiting, fainting, hallucination, perspiration, skin disorders, spasmodic pain, hyperlipidemia, burning sensation, delirium, anorexia, ill health, weakness, impotency, leads to lack of complexion and even death.	Powder of *Coriandrum sativum* (*Dhanyaka*) fruit or *Sesbania grandiflora* (*Munivrihi*) should be given repeatedly along with sugar candy (*Sita*).
Iron (Lauha)	Aphrodisiac, anti-ageing, emaciating, immunomodulator properties, increases potentiality, complexion and appetite. It eradicates diseases caused by vitiated *Kapha* and *Pitta*.	Anemia, diabetes, tuberculosis, piles, skin disorders, worm infestation, cachexia, obesity, bowel syndrome, splenic disorders, hyperlipidemia, dyspepsia, spasmodic pain, and also in poisoning.	1/4th to 2 *Ratti* (30 to 250 mg)/ day.	Angina, skin disorders, urolethiasis, spasmodic pain, burning sensation, weakness and even death.	Powder of *Embelia ribes* fruit should be given repeatedly with the Juice of *Sesbaniagrandi flora* leaves and patients should be exposed to sunlight. If worm infestation

					occurs, then patient should be purgated by giving the fruit pulp of Cassia fistula. If patients complain of spasmodic pain, then *Abhraka Bhasma* and Powder of *Embelia ribes* fruit with juice of *Embelia ribes* fruit or Powder of *Elletoria cardamomum* seeds should be given repeatedly.
Tin (*Vanga*)	Aphrodisiac, rejuvenator, appetizer, digestive, immuno-modulator properties, increases potentiality, complexion, and intellect. It eradicates diseases caused by vitiated *Kapha* and *Pitta*.	Diabetes, hyperlipidemia, anemia, dypnea, cough, ophthalmic disorders, worm infestation, emaciation, flatulence and in oligospermia.	1 to 2 *Ratti* (125 to 250 mg) / day.	Diabetes, skin disorders, abdominal tumor, cardiac diseases, spasmodic pain, piles, gout, goiter, cough, dyspnea, weakness and vomiting.	Powder of *Mesashringi* (*Gymnema sylvestre*) fruit should be given with sugar candy repeatedly for 3 days.
Zinc (*Yasada*)	Ophthalmic nourisher, immunomodulator, increases strength, potentiality, and intellect. It alleviates diseases caused by vitiated *Kapha* and *Pitta*.	Diabetes, anemia, dyspnea, cough, emaciation, ulcer, depression, tremor, ophthalmic disorders etc.	½ to 1 *Ratti* (60 to125 mg)/ day.	Diabetes, indigestion, vomiting, hallucination etc.	Powder of green *Terminalia chebula* (*Vala Haritaki*) should be given repeatedly along with sugar candy (*Sita*) for 3 days.

Permissible Limits for Heavy Metals in Various Regulatory Guidelines According to Ayurvedic Pharmacopoeia [38]

Table 4: Permissible Limits According to Ayurvedic Pharmacopoeia

S.No.	Heavy Metal contents	Permissible limits
1.	Lead	10 ppm
2.	Arsenic	3 ppm
3.	Cadmium	0.3 ppm
4.	Mercury	1 ppm

Examples of national limits for arsenic and toxic metals in herbal medicines and products (WHO guidelines) [39]

Table 5: Permissible Limits According to Who Guidelines

		Arsenic (As)	Lead (Pb)	Cadmium (Cd)	Chromium (Cr)	Mercury (Hg)	Copper (Cu)	Total toxic metals as lead
For herbal medicines								
Canada	Raw HM	5 ppm	10 ppm	0.3 ppm	2 ppm	0.2 ppm		
	Finished HP	0.01 mg/day	0.02 mg/day	0.006 mg/day	0.02 mg/day	0.02 mg/day		
China	HM	2 ppm	10 ppm	1 ppm		0.5 ppm		20 ppm
Malaysia	Finished HP	5 mg/kg	10 mg/kg			0.5 mg/kg		
Republic of Korea	HM							30 ppm
Singapore	Finished HP	5 ppm	20 ppm			0.5 ppm	150 ppm	
Thailand	HM and Finished HP	4 ppm	10 ppm	0.3 ppm				
WHO recommendations (2)			10 mg/kg	0.3 mg/kg				
For other herbal products								
National Sanitation Foundation draft proposal (Raw DS)[a]		5 ppm	10 ppm	0.3 ppm	2 ppm			
National Sanitation Foundation draft proposal (Finished DS)[a]		0.01 mg/ day	0.02 mg/day	0.006 mg/day	0.02 mg/day	0.02 mg/day		

[a]Dietary supplement; HM: Herbal Materials; HP: Herbal Products; DS: Dietary Supplement

Permitted Daily Exposures and Permitted Concentrations for Elemental Impurities [ICH Guidelines] [26]

Table 6: Permissible Limits According To ICH Guidelines

Element	Class	Oral Route µg/day		Parenteral Route µg/day		Inhalation Route µg/day	
		PDE	PC	PDE	PC	PDE	PC
As	1	15	1.5	15	1.5	1.9	0.29
Cd	1	5.0	0.50	6.0	0.60	3.4	0.34
Hg	1	40	4.0	4.0	0.40	1.2	0.12
Pb	1	5.0	0.50	5.0	0.50	5.0	0.50
Co	2A	50	5.0	5.0	0.50	2.9	0.29
Mo	2A	180	18	180	18	7.6	0.76
Se	2A	170	17	85	8.5	140	14
V	2A	120	12	12	1.2	1.2	0.12

PDE: Permitted daily exposure

PC: Permitted Concentrations of Elemental Impurities in drug products, drug substances and excipients with daily doses of not more than 10 grams per day.

Acceptable limits for elemental impurities according to Quality of Natural Health Products Guide, Canada. [40]

Table 7: Permissible Limits According to Quality of Natural Health Products Guide, Canada

Element	Adult Limit per day	Limit per day per kg body weight	Limit in parts per million (ppm) for Topical Products
Total Arsenic	< 10.0 µg/ day	< 0.14 µg/kg b.w./day	3 ppm
OR Inorganic Arsenic	< 2.1 µg/ day	< 0.03 µg/kg b.w./day	
Organic Arsenic	< 1.4 mg/ day	< 20 µg/kg b.w./day	
Cadmium	< 6.0 µg/ day	< 0.09 µg/kg b.w./day	3 ppm
Lead	< 10.0 µg/ day	< 0.14 µg/kg b.w./day	10 ppm
Total mercury	< 20.0 µg/day	< 0.29 µg/kg b.w./day	1 ppm
Methyl mercury	< 2.0 µg/day[a]	< 0.029 µg/kg b.w./day[a]	
Antimony	-	-	5 ppm

a- Methyl mercury determination is not necessary when the content for total mercury is less than the limit for methyl mercury.

Established oral limits for toxic heavy metals by various organizations [40]

Table 8: Permissible Limits According to Various Organizations

		Established oral limits (µg/day)			
		Arsenic	**Cadmium**	**Lead**	**Mercury**
Limit for finished product: daily dose	AHPA (American Herbal Products Association)	10	4.1	10	2.0
	NSF(National Science Foundation) /ANSI 173 (American National Standards Institute ANSI 173)	10	6	20	20
	Canada Natural Health Products Directorate	10	6	20	20
	California Prop 65 Reproductive Toxin	None set	4.1	0.5	-
	California Prop 65 Carcinogen	10	-	15	-
Limit for total daily consumption	US Agency for Toxic Substances and Disease Registry (ATSDR)	20	14	-	20
	US Environmental Protection Agency (EPA)	20	70	-	7
	US FDA Tolerable Daily Intake	130	55	75	-
	Joint FAO/WHO Expert Committee on Food Additives (JECFA)	150	70	250	16
	European Union	-	70	250	16

CONCLUSION

Herbal medicinal products are consumed by a wide range of the world population of which some contain toxic materials such as heavy metals either as a therapeutic agent or as a contaminant. The presence of heavy metals above the prescribed limits 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. The Rasa-Shastras should be thoroughly studied and its principles should be implemented for proper processing of heavy metals in these medicines. Today patients indulge in self-medication without proper prescriptions, which should also be checked and discouraged.

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