

REVIEW ARTICLE

# Toxicological Aspects of Ayurvedic Medicines: A Review

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## ABSTRACT

Ayurvedic medicine is considered to be one of the oldest medical systems in the world, and it is based on the ancient Indian medical philosophy i.e. depend on a “natural” and holistic mental and physical health approach and it remains one of the mainstream health care systems in India. Ayurvedic medicines are very popular in India and other Asian & Western countries as an alternative to chemical medicines because of their no / very few side effects on the human body. Ayurvedic medicines are known for the treatment of chronic diseases such as cancer, diabetes, arthritis, and asthma. This paper describes the possible causes for the various types of toxicity occurring/reported due to the intake of different types of Ayurvedic bhasma (nanoparticles) and herbal medicines, among them heavy metal toxicity (Lead, Mercury, Arsenic) is commonly seen. Many medicinal plant preparation could interfere with the proper functioning of certain medicines like Phenobarbital, Alprazolam, etc. The contamination of Herbal Medicines from heavy metals or microbial toxins can lead to nephrotoxicity, neurotoxicity, Hepatotoxicity, and severe damage to other body organs. Due to nonavailability of proper data on short, medium, and long term usage of Ayurvedic Bhasmas, heavy metal toxicity has been reported. Ayurvedic Bhasmas are safe though a lack of standard protocol or method of preparation.

**KEYWORDS** | heavy metals, toxicity, ayurvedic medicine, rasa shastra

## INTRODUCTION

AYURVEDIC MEDICAL SYSTEM is considered to be one of the oldest medicine systems in the world, originating in India during the 2000-1000BC. Ayurveda began to spread to other countries such as China, Sri Lanka, and Mongolia during the 6th century BC through the Buddhist monks traveling around the world.<sup>1,2</sup> Ayurvedic medicines are prepared from herbs, minerals, and animal derivatives such as horn, shells, feathers etc., both as single-ingredient drugs and as composite formulations. Typically, the formulations are divided into two groups, based on plants & minerals (Bhasmas), such as Shankh Bhasma, Hartal Bhasma, etc.<sup>3</sup> They are available in a variety of forms: tablets, pills,

liquids, and semi-solid forms. Ayurvedic medicines extracted from plant extracts are usually considered safer, with no side-effects. There are various benefits of Ayurvedic medicines over allopathic medicines such as preserving the quality of life or developing a natural immune system. In today's COVID-19 pandemic times, most of the medicine systems have failed to provide a cure, whereas several formulations of Ayurvedic medicines, which are centuries old, have been popular worldwide have been helpful in boosting the immune system to fight against COVID pandemic.<sup>4</sup> But the view starts to change when Ayurveda, India's ancient system of medicine, is accused of toxicity in its medicines as many cases

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of severe toxicity due to intake of Ayurvedic medicines have started to surface.<sup>5</sup>

#### LITERATURE REVIEW

Several studies were performed on Ayurvedic medicines which were reported to have various amount of heavy metals in their formulations. A study was conducted in 2005 where 230 Ayurvedic medicines bought via the internet in the US and India, were randomly selected for analysis using an instrumental technique like X-ray fluorescence spectroscopy and it was recorded that nearly one-fifth of US and Indian-manufactured Ayurvedic medicines contain detectable lead, arsenic or mercury. All Ayurvedic medicines exceeded one or more standards for acceptable daily intake of toxic metals.<sup>6</sup> As per a media report in the USA, the New York City Health Department has asked the citizens to stop taking Ayurvedic medicines of Indian pharmacies as they were claimed to contain elevated levels of lead and mercury, which make it unsafe for human consumption.<sup>7</sup> The Houston Department of health services has detected lead and arsenic in seven South Asian traditional medicines and warned its residents against using these medicines.<sup>8</sup> In Another report of 2005, Health Canada has disapproved certain Ayurvedic products in the Canadian market due to detection of elevated levels of lead, mercury, and/or arsenic. It also warned consumers against buying these Ayurvedic products.<sup>9</sup> An incidence of death was reported when a person developed sub-acute toxicity after taking Dahana Bhasma prescribed for dyspepsia and appetite enhancement which ultimately led to his death. His death occurred after he took Ayurvedic Bhasma which had no labeling of ingredients. The said patient's case history also revealed that he had no habit of alcohol or any other recent medication taken apart from Vitamin B and Vitamin D.<sup>10</sup>

Kava, an herbal sedative prepared from plant (Piper methysticum), was found to have anti-anxiety or calming effects. It has been reported that the patient who was on a medication of Terazosin, Cimetidine, and Alprazolam, became disoriented and lethargic after ingesting Kava. A case has been reported in which severe hepatitis was seen in patients due to the use of Kava, as a result of which the patient eventually needed a

liver transplant. Hence FDA issued an advisory and warned the public against the use of this medicine.<sup>11-13</sup>

Comfrey is a perennial herb that is used in the preparation of herbal medicines. Pyrrolizidine, an alkaloid present in its roots has shown hepatotoxic effects in animals and humans that can also induce tumors. Various studies show that Phenobarbital, a barbiturate, could induce the metabolism of pyrrolizidine alkaloids and convert it into a lethal metabolite. Some studies reveals that hepatic-veno-occlusive disease is related to the in-take of Comfrey.<sup>14-16</sup> The case study of a 70-year-old man who reported bleeding from the iris into the anterior chamber of the eye after one week of starting a self-prescribed regimen of medication of concentrated ginkgo biloba extract of 40 mg twice a day.<sup>17</sup> Hypertension was commonly seen, the adverse reaction was followed by a steep rise in heartbeat, tachycardia, strokes and even seizure. In some cases death has also been reported.<sup>18,19</sup> Various cases of unexpected lead poisoning due to the use of herbal medicines contaminated with lead have been reported. A case of acute porphyria was reported in a 23-year-old male. In his urine the porphyrin was seen positive indicating acute porphyria. Later on further examination lead (77ug/dL) was detected in his body. Another case of lead-poisoning occurs after taking Chinese medicine Cordyceps in which the lead content was found higher than 20000 ppm.<sup>20, 21</sup> Several case studies related to herbal medicine toxicity have been discussed herein which the drug or herbal medicine caused side effects after taking it for treating a particular disorder/disease. A report describes progressive renal failure in a forty-year African male after consuming a drug named Pausinystalia yohimbe which is an herb.<sup>22</sup> Chronic renal failure has been reported after taking Chinese herbal medicine Panax ginseng (Renshen Yangrong Tang), which is used for treating anorexia & hypoproteinemia. Cardiotoxicity and renal toxicity reported after consuming Tripterygium wilfordiiian, an herb used for treating Arthritis.<sup>23</sup> Cases of neurotoxicity and liver toxicity were also reported after consuming an herbal medicine containing the herb Valeriana officinalis which is a popular sedative agent.<sup>24</sup>

It has also been seen that in a number of cases

interference in the functioning of an allopathic drug like Hyper perforatum interferes with Alprazolam<sup>25</sup>, Ginkgo biloba interferes with sodium valproate<sup>26</sup>, Panax ginseng interferes with Phenelazine<sup>27</sup>, Cimicifuga interferes with Atoravastatin<sup>28</sup>, Seutelluariae interferes with Losartan<sup>29</sup>, Evolvulus alsinoides interferes with Phenytoin<sup>30</sup>, Allium sativum interferes with Saquinavi.<sup>31</sup> This paper discusses the recent studies on Ayurvedic medicines and possible causes of their toxicity.

The Ayurvedic medicines are categorized into two types as *rasa shastra*, and *non-rasashastra*, both of which differ in their preparations.

### Herbal Medicines

Herbal drug (Herbal medicine) is considered to be the entire or grained, desiccated part of a plant, algae, lichen, fungi, which is useful due to its medicinal properties. Both plant organs (flower, fruit, bark, root, seed, and leaf) and plant exudates like rubber, balsams, and resins can also be considered as Herbal medicine preparations. Herbal drugs are prepared from herbs, by following procedures of distillations, extraction and filtration, and a few more steps.<sup>32</sup> Various types of herbal medicines commonly available in the market are Echinacea, Ginseng, Ginkgo, biloba, Elderberry, Valerian, Camomile, Ashwagandha capsules, Cardimap, and many more. As per WHO, herbal drugs are classified into four different classes based on their origin, mode of current usage and evolution:

*Indigenous Herbal Medicine:* Used historically in a local community or region, it is very common among the local population for a very long time in terms of their composition, dosage, and treatment.

*Herbal Medicine in System:* These are in Ayurveda, Unani, and Siddha, some indigenous herbal medicines are now available in the market and are popular in the region or local community now, but it's important to fulfill the standards and requirements as per regulations for safety and efficacy of herbal medicine.

*Modified Herbal Medicine:* These are altered or modified in terms of compositions, Medical indications shape, methods of preparation, ingredients, dose, mode of administration, and dosage form also.

*Imported product with an herbal medicine base:*

Include the raw material and products, the importing country and recipient country should ensure that the medicines meet the national regulatory requirements of exporting country as well as receiving country.

### Major Causes of Toxicity

The toxicity caused by herbal medicines can be related to two major factors, direct (Intrinsic) and indirect (Extrinsic).

*Intrinsic Factor:* In orthodox medicine, the toxic effects are classified into four major categories in the same way toxic effects of the herbal medicines can be classified into four categories.

**Type A (acute augmented)** includes interaction with pharmaceuticals or overdose. It is connected with the integral pharmacological properties of herbal products; substance is poison or remedy depends on the dosage. Herbal medicines have been established to be an effective remedy for thousands of years, overdose or inappropriate or wrong consumption could lead to adverse drug effects. Different body organs and systems may get affected due to adverse drug effects.

**Type B (bizarre/idiosyncratic)** reactions are common adverse reactions triggered by herbal products which range from minor allergic reactions to severe anaphylactic shock. Its examples include Anaphylaxis and hives, acute asthma.

**Type C (chronic/cumulative)** reactions occur due to long-term therapy or use that are well known and anticipative or expected. Its examples include Hypokalemic paralysis that occurs after ingesting Licorice for a long period.

**Type D (delayed)** is not commonly reported due to the nonexistence of systemic assessment for herbal medicine, Delayed effects because of herbal medicines become more apparent in the future. Its examples include carcinogenesis which is associated with the Aristolochia species due to the presence of aristolochic acid. These herbal remedies are generally prescribed as a mixture of some medicinal plants and commonly taken as complementary medicine with conventional ones. The toxicity may occur when they are simultaneously present, which could occur differently like pharmacokinetic interaction which may change absorption, metabolism, distribution, and excretion of the drug and altering therapeutic/

beneficial properties also pharmacodynamics interaction affects the molecular target that intermediates various physiological responses.

#### **Extrinsic Factor**

The Extrinsic Toxic effects are related to contamination, misidentification, and adulteration of herbal medicines. It has been observed that lack of proper quality control of preparation & production of these herbal medicines' contamination with heavy metals and some toxic microbial substances has been reported worldwide.

*Heavy metals:* The commonly found heavy metals in herbal medicine are arsenic (As), mercury (Hg), lead (Pb), and cadmium (Cd). They are a serious public health concern because of their toxicity even at very low concentration. The contamination due to heavy metal in herbal medicines is a major concern in various Asian countries. The source of heavy metal contamination in herbal medicines could have come during the growth, development, processing of these herbal medicines. Medicinal plants could accumulate these heavy metals from agricultural soil, water, fertilizers and pesticides used. Also from air pollution. As a result of these, the WHO, which also regulates the permissible limits of toxic metals, has advised detecting the presence of these heavy metals in the raw materials that are used for the final product.

*Microbial Toxins:* The concern of microbial toxins in herbal products is also increasing worldwide even after so much research on bacterial, and fungal contamination on food is done. Mycotoxins (a type of microbial toxin), Aflatoxins, fumonisins, ochratoxin A, zearalenone, and deoxynivalenol have been reported in various medicinal plants globally.

*Adulteration:* The addition of some drugs or substances which are not labeled or due to improper preparation of herbal medicines requires heavy metals as an ingredient. As adulterants are not labeled on the ingredient listed it increases the chances of overdose and interactions, and serious outcomes.

*Misidentification:* Due to confusing nomenclature, similar appearance, and complication in processed products of herbal remedies and medicinal plants, a case has been reported in which a 23-year-old lady was hospitalized when she suffered a

complete blockage of the heart after ingesting an herbal product, Chomper, due to the replacement of (*Plantago major*) Plantain with (*Digitalis lanata*) Woolly foxglove in the herbal product due to the similarity of a leaf.<sup>33</sup>

#### **Ayurvedic Bhasma**

On other hand, Ayurvedic Bhasma is considered to be ancient forms of nano medicine. Bhasmas are considered to be unique Ayurvedic metallic/mineral preparations that are treated with herbal juices or decoction and exposed to a certain degree of heat. Bhasmas are prepared by two methods putapaka and kupipakwa. The Bhasma is prepared by exposing metals or minerals to a three-step procedures that are (Shodhna, Bhavana, Marana).<sup>34</sup> This procedure is repeated continuously for a certain specific period of time. Finally, the prepared Bhasma is collected. The repetition of the process of incineration reduces particle size and it is observed that after passing all these stages, the Bhasma becomes biologically favorable for the body and thus it is seen that after the formation of Bhasma it passes through various parameters for quality of Bhasma. Rasa shastra method for preparing Ayurvedic Bhasma is considered for therapeutic use.<sup>35</sup> Rasa shastra claims that the inorganic form of mercury, which is toxic, can be converted into Rasa sindura, which is safe. Bhasma and various traditional medicines are forwarded to a process known as "alchemy" which alters the mineral form which is generally suitable for the medication (i.e. HgS, PbS, PbO, As<sub>2</sub>S<sub>3</sub>) which are different from the environmental metal contaminants like (NaAsO<sub>2</sub>, AsO<sub>4</sub>, HgCl<sub>2</sub>).<sup>36</sup> The particle size of these bhasmas are determined by various techniques such as Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Cryo TEM, Confocal laser scanning microscopy, Energy dispersive X ray (EDAX), X-ray induced photoelectron spectroscopy, and quantization of different heavy metals in Bhasma by Inductively Coupled plasma (ICP), Atomic absorption spectroscopy (AAS ).<sup>37-40</sup> The metal poisoning cases especially of lead (Pb), Arsenic (As), Mercury (Hg) are on the rise because of inappropriate procedure followed during Bhasma preparation and inadequate testing. Therefore, pharmaco vigilance is required. The public health

influence of metals in Bhasma or rasa shastra in India is opaque and controversial, as Ayurveda claims that in India medicines produced by rasa-shastra process are safe and are in use for a long time, according to them the metal toxicity occurs due to inappropriate commercial manufacturing practices or else due to lack of proper monitoring by person skilled in rasa shastra. Ayurveda texts endorse proper detoxification processes in the preparation of Bhasma. The use of Bhasmas in such an era where enough studies on the short, intermediate and long-term use are not available, may pose a threat to the public.<sup>41</sup>

#### **Possible Toxic Effects of Heavy Metals in the Human Body**

Toxicity is a complex one with various influencing factors among them. Dosage is the most significant one. Toxicity is the outcome of various changes like macromolecular one, Biochemical, and Adverse cellular. Cell replacement which is seen in fibrosis, production of reactive chemicals, interruption of protein synthesis, Enzyme system damage, and even DNA damage are generally encountered in case of toxicity.<sup>42</sup>

#### **Physiological Classification of Toxic Responses**

The type of physiological effects they have on the human body so toxic substances can be classified as Teratogens (lead), Mutagen, Carcinogen, Reproductive toxins (lead), Pulmonary toxins (chromium), Hematopoietic Toxin, Neurotoxins (lead), Nephrotoxins (mercury), Hepatotoxin, Anesthetic, Asphyxias, Corrosive, Irritants.

#### **Biochemical Effects of heavy metals**

We will discuss the most toxic heavy metals and which are found in Ayurvedic preparations are arsenic, lead, mercury which can cause toxicity even in smaller doses.

*Arsenic (As):* This is considered the most toxic metal; exists in three valence states (0,+3,+5) called metalloids arsenic (with 0 oxidation state), arsenates (+5), arsenite (+3). The acute toxicity may result in fever, liver enlargement, anorexia, and even death. Various health effects of arsenic toxicity are due to chronic exposure that may produce poisoning of the nervous system, and severe liver damage, gangrene of the lower limb (Black Foot disease) which is a result of peripheral vascular disease. Major biochemical effects which lead to tissue respiration impaired that are:

*Complexation with coenzymes/enzymes-* Arsenic (+3) disrupts sulfhydryl containing enzymes by binding with (-SH) groups, which results in the inhibition of necessary metabolic activities of cellular respiration like stoppage of Tricarboxylic acid cycle (TCA), succinate, and pyruvate oxidation pathways which ultimately lead to no synthesis of ATP which is an important source of energy in the human body, this inhibitory action occurred due to inactivation of enzyme pyruvate dehydrogenase by As (+3) ion.

*Coagulation of Proteins-Arsenic (+3)* compounds attacks the sulfur bonds which are necessary for the primary & secondary structure of proteins.

*Uncoupling of Phosphorylation:* An alternate pathway is by substitution of as (+5) for phosphorus, due to its chemical similarity with phosphorus. The phosphorus anion in phosphate is a stable anion which is substituted by less stable as (+5) anion as a result of which there is speedy hydrolysis of high energy bonds in different compounds like ATP, as a result, loss of high energy phosphate bonds occurs and “uncouples” the process oxidative phosphorylation.

*Mercury (Hg)-* It exists in three forms metallic mercury (elemental mercury), inorganic & organic mercury. Various forms in which mercury occur naturally in the surroundings like metallic mercury, mercury sulfide (cinnabar), mercuric chloride, methyl mercury. Metallic mercury is not as toxic as methyl mercury due to slow absorption through the gastrointestinal tract various health effects of mercury toxicity depend upon its form which affects different parts of the body. Organic mercury (Methyl mercury) affects CNS and produces neurotoxic effects in adults and causes toxicity in the fetus of pregnant women, Inorganic mercury (mercuric salts) causes toxicity in the kidney it can also lead to abdominal cramps and bloody diarrhea.

Major biochemical effects of mercury are due to binding with sulfhydryl group or thio group which leads to interference in protein synthesis, and a strong affinity for sulfur which makes it easily bind to any compound containing sulfur or sulfur hydrogen combination

*Elemental Hg (mercury):* It is commonly found in liquid form, also is easily vaporized even at the room temperature and can be absorbed mostly

through inhalation, Mercury vapors inside cell converted into mercury (+2) which is more toxic form. This divalent form of mercury is responsible for causing erethism (mad hatter's disease).

**Inorganic Hg (mercury):** It is commonly found in mercuric salt form and is highly corrosive. It enters in body dermally or orally and gets stored in the kidney. In the GI tract, it causes sloughing away of the mucosa, even the pieces are found in stools.

**Organic Hg (mercury):** It has a high affinity to lipids, Alkyl organic mercury gets deposited into hair, nail, liver, kidney, brain. They also show teratogenic effects due to crossing blood placenta barriers, also crosses the blood-brain barrier, and also can easily penetrate erythrocytes' leading to neurological symptoms.

**Lead (Pb)** It is the most widely spread Toxic metal. Lead usually enters into human body from contamination like lead pipes or lead solder. Children are more vulnerable to lead poisoning because it absorbs more readily in growing bodies. It causes various abnormalities related to bone growth in children. It majorly affects three organ systems

**Neurological System:** In CNS it alters the functioning of cellular calcium leading to inhibition of the blood-brain barrier. This is followed by leakage of proteinaceous fluid and brain edema, which affects mainly the occipital lobe, cerebellum. This edema is manifested initially by headache, clumsiness, vertigo, ataxia leads to seizure, coma death or sometimes recovery is their permanent neurological loss.

**Hematological System:** It has a major effect on heme synthesis. Any compound having a

sulfhydryl group is can be easily disrupted by lead. Lead crosses the blood-brain, placenta barrier and can easily be deposited into soft and hard tissue of the body.

**Renal Effects:** It causes irreversible nephropathy due to functional impairment of tubular regions characterized by glucosuria, Hyperphosphaturia.<sup>42</sup>

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#### DISCUSSION

Natural medicine is safe but contrary to popular belief, herbal medicine can cause severe health problems and even death in some cases. Many medicinal plant preparations could interfere with the proper functioning of certain medicines like Phenobarbital, Alprazolam, etc. The contamination of herbal medicines from heavy metals or microbial toxins can lead to nephrotoxicity, neurotoxicity, hepatotoxicity, and cause severe damage to certain body organs.

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#### CONCLUSION

Ayurvedic bhasmas are generally considered safe, as they are prepared in accordance with instructions mentioned in ancient Ayurvedic texts, but due to lack of standard protocol or method of preparation, these bhasmas are found to be a threat to public health due to the presence of heavy metal toxicity in them as there is a lack of proper data on short, medium and long-term usage of these bhasmas. **IJFMP**

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