ISSN 2581-6217

World Journal of Pharmaceutical Science & Technology

Journal homepage: www.wjpst.com

REVIEW ARTICLE

A REVIEW OF HEAVY METAL TOXICITY STUDIES IN CONTEXT WITH *NAGA BHASMA*

Dr. Dinesh Kelgaonkar[1], Dr. (Prof.) Rajesh Ingole[2]

1. Ph.D Scholar, Department of Rasashastra & Bhaishajya Kalpana Government Ayurved College and Hospital, Nanded
2. Professor and H.O.D, Department of Rasashastra & Bhaishajya Kalpana Government Ayurved College and Hospital, Nanded

Address for correspondence:

Dr. Dinesh Kelgaonkar: Ph.D Scholar, Department of Rasashastra & Bhaishajya Kalpana Government Ayurved College and Hospital, Nanded

E-mail Id:- **dkelgaonkar@rediffmail.com**

Received: 12-02-2024, Revised: 10-03-2024, Accepted: 16-04-2024

ABSTRACT

Introduction: The well known metal mostly used in Ayurveda includes mercury, gold, silver, copper, arsenic, lead and tin. The review of ancient Rasa literature revealed that the ancient Rasaacharyas have recognized doshas (untoward effect) in almost all drugs including metals, minerals and mercury. To remove these untoward effects they have described suitable techniques and procedures such as Shodhana, Marana etc and these processes were used to convert the metal and minerals in to the pharmaceutically suitable and ideal forms. Harmful heavy metals are difficult to excrete from the body if people particularly have chronic illnesses**.** are toxic or not. **Result:** The APO-E 4/3 and 4/4 genotypes have been found to be the worst excretors of heavy metals. The highest propensity for developing neurological problems from exposure to neuro-toxic heavy metals, especially mercury when it is present in combination with other metals, will be found in those with this variant of APO-E protein abundant in cerebral spinal fluid surrounding the brain. **Conclusion:** The elaborate preparation protocol involved in the traditional medicines is believed to modify the toxic nature of the precursor (metal) and adds therapeutic value. Many factors such as preparation based factors, chemical nature based factors, vehicle used, therapy associated factors, pharmacological factors, etc, determine whether the traditional

medicines

Keywords: Lead toxicity, Metal toxicity, *Naga bhasma*

1. INTRODUCTION

The pharmacological section of Ayurvedic system of medicine recognizes three major sources of medicine, those of herbal origin (e.g. herbs), mineral origin (e.g. salts, metals like gold, copper, silver), and animal origin (e.g. milk, honey etc). Although, Kashthaushadhis and Rasaushadhis are two main groups of medicines, the former is devoid of any metals and minerals and is purely herbal product and can be considered as safest of medicines, and later consists of metal and minerals in the form of Bhasma (incinerated metal, minerals etc.). These metallic preparations occupies significant seat in Ayurvedic pharmacopoeia. The well known metal mostly used in Ayurveda includes mercury, gold, silver, copper, arsenic, lead and tin. These metals have specific gravity more than five hence these are categorized in group of heavy metals. Accumulated toxicity data on the hazardous effects of heavy metals have made health scientists afraid of heavy metals. As a result, renewed interest in the beneficial effects of metals and minerals is often viewed with skepticism. Many people's which are unaware of the pharmaceutical processing of Rasaushadhis (bhasma and other herbo-metallic preparations), are in doubt about their safety and efficacy.[1]

Use of metals and minerals for the medicinal purpose was prevalent even in prehistoric period but to a very limited extent. It is also clear from the literature, that in earlier times, these drugs were used either in the form of fine powder or as paste after rubbing. The more suitable forms were developed after the evolution of Rasashastra. The review of ancient Rasa literature revealed that the ancient Rasaacharyas have recognized doshas (untoward effect) in almost all drugs including metals, minerals and mercury. To remove these untoward effects they have described suitable techniques and procedures such as Shodhana, Marana etc and these processes were used to convert the metal and minerals in to the pharmaceutically suitable and ideal forms. For most of the metals, methods of bhasma preparation as given in the classical texts differ between themselves in terms of accompaniments and process detail. Correspondingly, the processing of certain metals lead to bhasmas with different forms and colors. Based on their experiences, the ancient Acharya's described many methods for Shodhana, Jarana and Marana of metals and minerals depending on the therapeutic utility of respective metal; compounds prepared through these processes are considered as pharmaceutically most suitable forms, hence it is important to know the various ways of processing the single metal.

Bhasmas are special Ayurvedic metallic formulations with herbal juices or fruits that are frequently used to treat a range of chronic illnesses.[2] Naga bhasma which is obtained from metallic lead, is a miraculous Ayurvedic drug and used in various diseases such as diarrhea, spleen enlargement and diabetes.[3] Although, the therapeutic efficacy of Naga bhasma changes with change in the preparative procedure e.g. Naga bhasma prepared by triturating with juice of Ahiphen (Papaver somnifera) possesses more aphoristic property while the Naga bhasma prepared from Manashila, Gandhaka and Vasa (Adhatoda vasica) is more effective in skin diseases.[4] Thus, the method of preparation and drug used in preparation of drugs has significant importance in

defining its mode of action, its absorption and action on the body. This articles is designed with perspective to review different studies on heavy metal toxicity studies in context with *Naga Bhasma*.

2. MATERIALS AND METHODS:

Data and information pertaining to toxicity of *Naga bhasma* and its toxicity were searched from text books, journals, web-based search engines source were referred for research data and presented in systemic manner.

3. RESULT:

Definition

Chemical elements with a specific gravity that is five times greater than that of water are referred to as heavy metals.[5] The excessive accumulation of heavy metals in the body is referred to as heavy metal toxicity.[6] Since the body cannot break them down, they accumulate in body tissue, interfere with normal system operation, and may cause diseases like Alzheimer's, Parkinson's disease, muscular dystrophy, and multiple sclerosis.[7]

Bhasma and heavy metals:

Trituration of curd leads to formation of ghee but it doesn't mean that curd is ghee. Similarly bhasma are prepared from heavy metals but they are not heavy metal. Sanskara (processing) brings significant difference in the initial and final material. Before using metals for therapeutic purpose Ayurveda clearly advised to conduct some procedures which are known as shodhana (purification). After purification the metals and minerals are subjected to repeated cycle of incineration followed by triturating with some herbal juices. Thus the formed product is a herbometallic incinerated form (bhasma) with new physical and chemical properties. Heavy Metals as popularly explained metals with specific gravity greater than 5 gm/cm which means when they are put on to the water they will settle at the bottom. But going by the tests bhasmas for the final approval to use on the human beings must have following three qualities Varitar (they should float on water), Unnam (they should be able to take the weight of a rice grain, more weight bearing must be a critical change for the metals), Rekhapurna (they should have microfiness to fit into the lines of the hand and should not glitter), Niruttha (metal should not gain its crystalline form after heating with ghee, seed of Abrus precatorius, honey, borax and extract of comifora mukul). It clearly indicates that in the process of repeated incineration the previous metal get completely destroyed (that's why ancient achary named this process as marana means killing of metal) thus bhasma are not heavy metals, they are nanoparticles with a mixture of organic and inorganic compounds. E.g. lead has a low melting point 327.46 ̊C but the Naga bhasma (incinerated lead) didn't melt even at 800 °C and Naga bhasma is mixture of PbO, Pb_3O_4 and contain either OH, $(CO_3)_2$ or $(SO_4)_2$ and $(AsO_4)_3$.

Current research on Naga Bhasma and lead toxicity:

- Pravin tate et al.[8] conducted a work on acute and chronic toxicity of Naga bhasma. Acute toxicity study at LD50 which was 160 times higher to that of Therapeutic Equivalent Dose (TED) (12.5 mg/kg). In Chronic toxicity study, at a dose level TED x 05, and the overall toxicity study shows that both the test drugs do not produce significant toxicity at the dose level studied.
- Mrudula Wadekar et al.[9] conducted a comparative study of some representative samples of Naga bhasma from chemical and structural point of view by using XRD, IR and UV spectroscopy and thermogravimetry

is reported here . This study showed that the bhasama samples were predominantly crystalline i.e. mixture of PbO,Pb_3O_4. XRD data revealed OH and $(CO_3)_2$ group in all samples.

- According to an antidibetic research work on Naga bhasma carried out by Anjana Choube et al.,[10] the drug showed no untoward effect in any of the patients during and after the clinical study, ninety percent of the patients expressed sense of well-being and 70% of the patients showed improvement in the symptoms. 65% of the patients showed reduction in blood sugar and they were taking other hypoglycaemics also along with Sastiputa Naga bhasma. Fifty percent patients, those on Sastiputa Naga bhasma alone, showed reduction in blood sugar. This study revealed that Satiputa Naga bhasma can be recommended as a medicine and also as an adjuvant along with synthetic medicines for the management of diabetes mellitus.
- Singh Maksoodan et al.[11] studies on testicular regenerative potential of Naga bhasma. In this study it was observed that the test drug when given simultaneously with Cdcl2 showed marked prevention of toxic effects of Cdcl2 and when given alone after 36 hours of Cdcl2 administration, showed a noticeable regenerative potential on partially degenerated testes. It has showed specific regenerative effect on germinal epithelium of testes. Cdcl2 is toxic to testicular germinal epithelium and its effects can be minimized by Naga bhasma. In higher doses the drug is very effective, thus these findings are well collaborated with the Ayurvedic concept of vrishya property of Naga bhasma.
- S.K.Singh et al. carried out a significant work on synthesis, characterization and histopathological study of a lead-based Indian traditional drug: Naga bhasma. A higher dose (adopted in the animal experimentation) of 6 mg/100 g of body weight per day has been tried for the toxicity study. No significant changes were observed in histology as well as normal anatomy of the skin, small intestine, pancreas, testis, brain, lung, kidney and liver in bhasma-treated and untreated groups of animals, while in case of crude lead treated group of animals significant changes in certain organs were observed. Thus, histopathological studies show that Naga bhasma is non-toxic (6 mg/100 g/day), while crude lead (6 mg/100 g/day) is highly toxic. Thus it appears that in bhasmikarana process the crude lead is converted into Naga bhasma, which is found to be non-toxic at lower dosages.[i2]

Use of lead in Traditional Chinese and Tibetan Medicine:

Traditional Chinese Medicine (TCM) also has several lead-based preparations such as *Ba-pao-neu-hwang-san* that have been administered even to newborn children as well as adults (Chi et al., 1993).[13] Lead is used as an additive in several other TCM preparations and is termed as *mi tuoseng*. Classic Tibetan medicine uses certain metals like copper, white metal (75% lead, 19% antimony, 5% sulphur, and 1% copper) and brass which form the major constituents of a 'healing ring' (Clark, 1995, Donden, 2000).[14] According to Tibetan medicine practitioners, these three metals when worn can be used for common healing, balancing of essential energies, strengthening life energy, escalating circulation, regulating blood strain, and relieve ache (Clark, 1995).[15]

Lead toxicity[16]

Lead is a metallic irritant poison. As with other metals, the soluble compounds of lead are more poisonous than lead itself, except when lead is in the volatile state. Lead may obtain access to the body by inhalation, by ingestion, or by absorption from the skin or mucous surfaces. The primary effect of lead is to cause spasm of the capillaries and arterioles. The toxic effects result from fixation of lead in certain tissues such as brain and peripheral nervous system.

Acute lead Toxicity:

Infrequent and occurs from ingestion of acid-soluble lead compounds or inhalation of lead vapours. Symptoms are similar to arsenical or mercurial poisoning except that the stool is blackened and offensive. The principal manifestations are GIT and CNS disturbances. These are as follows:

- Astringent, thirst, and a metallic taste.
- Nausea, abdominal pain, vomiting.
- Stools may be black from lead sulphide, and there may be diarrhea or constipation.
- Shock.
- Paresthesias, pain, muscle weakness.
- Hemolytic crisis followed by severe anemia and hemoglobinuria.
- Kidney damage with oliguria.
- Death may occur in 1 or 2 days.

If the patient survives the acute episode, characteristic signs and symptoms of chronic lead poisoning are likely to appear.

Chronic lead Toxicity:

Lead poisoning is always of chronic type. Along with sources of ingestion described earlier, chronic lead poisoning may also result from the mobilization of lead already stored in the body tissues, especially the bones, eg, in acidosis, and symptoms of acute or chronic poisoning may develop, even years after the original absorption of lead. The signs and symptoms of chronic lead poisoning (plumbism) can be divided into six categories: gastrointestinal, neuromuscular, CNS, hematological, renal, and other. The neuromuscular and CNS syndromes usually result from intense exposure, while the abdominal syndrome is a more common manifestation of a very slowly and insidiously developing intoxication. The former is more common in children and later is more prevalent in adults.

Diagnosis of lead poisoning:

In the absence of a positive history of abnormal exposure to lead, the diagnosis of lead poisoning is easily missed. Furthermore the signs and symptoms of lead poisoning are shared by other diseases. For example, the signs of encephalopathy may resemble those of various degenerative conditions. Physical examination does not easily distinguish lead colic from other abdominal disorders. Clinical suspicion should be confirmed by determinations of the concentration of lead in blood and protoporphyrin in erythrocytes. Lead at low concentrations, decrease heme synthesis at several enzymatic steps. This leads to the buildup of the diagnostically important substrates δaminolevulinic acid, coproporphyrin (both measured in urine), and zinc

protoporphyrin (measured in red cells as erythrocyte protoporphyrin). Because the erythrocyte protoporphyrin level is not sensitive enough to identify children with elevated blood lead levels below 25 µg/dl, the screening test of choice is blood lead measurement. Children with concentrations of lead in blood above 10 µg/dl are at risk of developmental disabilities. Adults with concentrations below 30 µg/dl exhibit no known functional injury or symptoms; however, they will have a definite decrease in δ-ALA dehydratase activity, a slight increase in urinary excretion of δ-ALA, and an increase in erythrocyte protoporphyrin. Patients with a blood lead concentration of 30 to 75 µg/dl have all the above laboratory abnormalities and, usually, nonspecific, mild symptoms of lead poisoning. Clear symptoms of lead poisoning are associated with concentrations that exceed 75 Cdl of whole blood[17], and lead encephalopathy is usually apparent when lead concentrations are greater than 100 µg/dl. In persons with moderate to severe anemia, interpretation of the significance of concentrations of lead in blood is improved by correcting the observed value to approximate that which would be expected if the patient's hematocrit were within the normal range. The urinary concentration of lead in normal adults generally is less than 80 µg/liter. However, in persons with chronic lead nephropathy or other forms of renal insufficiency, urinary excretion of lead may be within the normal range, even though blood lead concentrations are significantly elevated. Neutron activation analysis or fluorometric assays, currently available only as research methods, may offer a unique in vivo approach to the diagnosis of lead burden in future.

Treatment of lead poisoning:

Metal toxicity was well known and well-documented in many *Rasashastra* texts, for example, for the treatment of lead toxicity. For three days, Acharyas recommended ingesting *Swarna Bhasma, Haritaki*, and *Sita* to counteract the negative effects of improperly prepared or underripe *Naga bhasma. Vishatinduka* was mentioned by *Rasataranginikara* as a remedy for *Nagadosha. Rasajirna's Nagadi Kalankita Rasa* was treated with *Gomutra, kutki*, and *Karavellaka Shifa* according to the *Rashridaya Tantra*.

In conventional science, Initial treatment of the acute phase of lead intoxication involves supportive measures. Prevention of further exposure is important. Seizures are treated with diazepam; fluid and electrolyte balances must be maintained; cerebral edema is treated with mannitol and dexamethasone. The concentration of lead in blood should be determined, or at least a blood sample for analysis obtained, prior to initiation to chelation therapy. Chelation therapy is indicated in symptomatic patients or patients with a blood lead concentration in excess of 50 to 60 µg/dl. Four chelators are employed: Edentate calcium disodium (CaNa2EDTA), Dimercaprol (British antilevisite; BAL), Dpenicillamine, and succimer (2, 3-dimercaptosuccinic acid; DMSA; CHEMET). In any chelation regimen, 2 weeks after the chelation has been completed, the blood lead concentration should be reassessed, an additional course of therapy may be advocated if blood lead concentrations rebound. Treatment of organic lead poisoning is symptomatic. Chelation therapy will promote the excretion of the inorganic lead produced from the metabolism of organic lead, but the increase is not dramatic.[18]

4. DISCUSSION:

Ayurvedic medicines best works if given after assessment of individual Prakruti (nature), Vikruti (Disease), Dosha - dushya sammurchana (gradation of disease process) and Sroto-dushti (tissues involved). It’s fairly

mentioned in classics that; a highly poisonous substance can prove to be an effective drug if used appropriately; conversely irrelevant or inappropriate use converts a good drug into a highly poisonous material. This suggests that possession of complete knowledge of the drug with regards to properties, dose, therapeutic action, rasa shudhi, shodhana, marana and preparation methods is very significant while assessing the toxicity effect of the drugs.

Harmful heavy metals are difficult to excrete from the body if people particularly have chronic illnesses**. Recent study shows that** those who cannot excrete heavy metals effectively may be genetically predisposed to severe conditions. The APO-E 4/3 and 4/4 genotypes have been found to be the worst excretors of heavy metals. The highest propensity for developing neurological problems from exposure to neuro-toxic heavy metals, especially mercury when it is present in combination with other metals, will be found in those with this variant of APO-E protein abundant in cerebral spinal fluid surrounding the brain. A heavy metal can enter the body from many different places. These sources include water, air, food, or skin absorption when in contact with people who have been exposed to toxic farming, chemical exposure, and toxic exposure in industries, among others.

Lead or plumbum (Pb) with an atomic number 82 can exist in divalent or tetravalent states and the divalent form (Pb^{2+}) is reported to be more stable. Lead induces toxicity in human body by inducing oxidative stress through generation of reactive oxygen species (ROS) or by depletion of antioxidant reserves (Ercal et al., 2001, Patra et al., 2001). Glutathione is an essential antioxidant, which can destroy the ROS.

The elaborate preparation protocol involved in the traditional medicines is believed to modify the toxic nature of the precursor (metal) and adds therapeutic value. Many factors such as preparation based factors, chemical nature based factors, vehicle used, therapy associated factors, pharmacological factors, etc, determine whether the traditional medicines are toxic or not. The toxicity of the metallic constituent is believed to be removed by the various heat and cool cycles in oil, buttermilk, rice gruel, cow's urine, herbal decoctions, etc. (Balaji et al., 2013).

The traditional medicine practitioners claim that the medication is personalized and hence should be consumed under the supervision of a practitioner since the concept of treatment is not symptomatic but rather a holistic approach. These circumstances show that any medication should only be administered after thorough understanding of the patient's body and the disease, which includes *prakriti* (individual personality), *dosha-dushya samurchhana* (involved organ and vitiated *dosha*), and *dhatu* (the seven basic body components mentioned in ayurveda). Moreover, a strict diet regime has to be adhered to during the treatment period (Sushant et al., 2012).

5. CONCLUSION:

Research works suggest that Incinerated Naga prepared by different methods are predominantly crystalline i.e. mixture of PbO, Pb_3O_4 and contain either OH, $(CO_3)_2$ or $(SO_4)_2$ and $(AsO_4)_3$ group. Acute and chronic toxicity study indicate that Naga is completely safe for therapeutic use especially Shastiputa Naga bhasma in diabetes. The testicular regenerative potential study elaborates the aphrodisiac property of Naga. The finished and

administered in accordance with the prescribed classical guidelines, ayurvedic herbo-metallic preparations, such as *Naga bhasma*, are secure and free from any significant adverse effects. It is past time to thoroughly test Ayurvedic herbo-metallic medications for their side effects, dose, duration, and toxicity in the body's intended target organ rather than merely prescribing them based solely on the text.

Further recommendation:

Although *Naga bhasma* and other lead based traditional medicine have been widely used for the treatment of diabetes, diarrhoea, spleen and skin disorders since ancient times, the scientific proof for the mode of action of lead in these medicines are lacking. The pharmacological studies to predict the effective concentration of lead in traditional preparation have not been carried out so far. In-depth studies at cellular and molecular levels are essential to understand the mechanism of toxicity. Animal studies are also necessary because they provide us with guidelines and enable us to address questions about how much *Rasaushadhis* should be used in relation to its safety margins.

COMPETING INTEREST

No competing interest exist as declared by author.

REFEERENCES

1. Dhirajsingh Rajput, Biswajyoti Patgir. Ayurvedic View on Heavy Metal Poisoning with Special Reference to Naga bhasma (Incinerated Lead) - A Literary Study. IJPBA, Vol. 4(1); 201 3:41- 45
2. Mrudula Wadekar et al. Comparative Study of some commercial samples of Naga Bhasma, Ancient science of life, Vol : XXIII (4) April, May, June (2004).
3. Rasaratna Samuchyaya, Kulkarni-Dudhgaonkar SB, Kolhapur: Shivaji University Publication; pp 158 (1970).
4. Rasoushadhi Nirmana, S. D. Kulkarni, Continental Publication Maharashtra Vidyapitha, Pune, 1st edition, 4th chapter, pp 93 (1981).
5. John H. Duffus., Heavy metals - a meaningless term (IUPAC Technical Report)" Pure and Applied Chemistry, 2002, Vol. 74, pp. 793–807.
6. Hogan M, E. Monosson, Clevel and C., Heavy metal - Encyclopedia of Earth. National Council for Science and the Environment. Washington, D.C. (2010).
7. http://www.patientsmedical.com/healthaz/ heavymetaltoxicity/ [Accessed on 2023 Sep. 20]
8. Pravin Tate et al. Pharmaceutical standardization & toxicity study of naga bhasma prepared by 2 different methods-madhumeha (diabetes mellitus),Dept of RS&BK, IPGT&RA, Jamnagar2008.
9. Mrudula Wadekar et al. Comparative Study of some commercial samples of Naga Bhasma, Ancient science of life, Vol : XXIII (4) April, May, June (2004).
10. Anjana Chaube, T.N Nagraja, S.K Dixit, J.K. Agrawal, Mohan Kumar and BHANU Prakash, A novel ayurvedic anti diabetic medicine, Ancient Science of Life, Vol No. XV2 October 1995, Pages 153-155
11. Sing M., Joshi D., Aryya N.C “Pharmaceutical and experimental study on Naga Bhasma with special reference to its toxicity & testicular regeneration” M.D (Ay.) Theses, B.H.U 1983:98- 113.

12. S. K. Singh, D. N. S. Gautam,1 M. Kumar,2 and S. B. Rai. synthesis, characterization and histopathological study of a lead-based Indian traditional drug: naga bhasma Indian J Pharm Sci. 2010 Jan–Feb; 72(1): 24–3
13. Donis-Keller H, Dou S, Chi D, Carlson KM, Toshima K, Lairmore TC, Howe JR, Moley JF, Goodfellow P, Wells Jr SA. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. Human molecular genetics. 1993 Jul 1;2(7):851-6.
14. Nagarajan S, Sivaji K, Krishnaswamy S, Pemiah B, Rajan KS, Krishnan UM, Sethuraman S. Safety and toxicity issues associated with lead-based traditional herbo-metallic preparations. Journal of Ethnopharmacology. 2014 Jan 10;151(1):1-1.
15. Loizzo JJ, Blackhall LJ. Traditional alternatives as complementary sciences: the case of Indo-Tibetan medicine. The Journal of Alternative and Complementary Medicine. 1998 Oct;4(3):311-9.
16. Parikh, Textbook of Medical Jurisprudence, Forensic Medicine and Toxicology, CBS Publishers & Distributors, New Delhi, 6th edition, 2000, 9.18-9.p. 24
17. National Research Council (US) Committee on Measuring Lead in Critical Populations. Measuring Lead Exposure in Infants, Children, and Other Sensitive Populations. Washington (DC): National Academies Press (US); 1993. 4, Biologic Markers of Lead Toxicity.
18. Boyd, A.H. Lower. Neutral fat of the perirenal depots. Can. J. Biochem. Physiol., 35 (1957), pp. 157-160.