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A CRITICAL REVIEW ON SAFETY AND THERAPEUTIC UTILITY OF ARSENIC COMPOUNDS MENTIONED IN RASASHSTRA

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ABSTRACT

Rasashastra is a unique branch of Ayurveda that utilizes various metals/minerals along with herbal drugs as medicines which are called Rasoushadhies. The science of Rasashastra has described different metals and minerals including heavy metals like Mercury, Lead, Arsenic for therapeutic usage. An article published in JAMA on 15th December 2004, stated the users of Ayurvedic medicines may be at risk of heavy metal toxicity. This made feel the necessity of safety data on metallo-mineral and herbo-mineral formulations used in Ayurveda. Conventionally, modern toxicology and pharmacology consider all the heavy metals like Arsenic as highly toxic. In this article an attempt is made to critically review the safety profile and therapeutic utility of Arsenic containing compounds explained in Rasashastra along with few of their important formulations.

KEYWORDS: Rasoushadhies, Arsenicals, Tala varga, Toxicity, Safety profile

INTRODUCTION

The use of Arsenicals as medicines is explained since the period of Brihatrayees and even before. 3 different compounds of Arsenic have been explained in Rasashastra. They are: Haratala (Arsenic Trisulphide), Manashila (Arsenic disulphide) and Gouripashana (Arsenous oxide). These are more often referred together as 'Tala varga'. In Rasashastra, the selection criteria (Graahya and Agraahya lakshanas), processing of drugs such as Shodhana/ purification, Marana (incineration), properties, therapeutic dosage, indications, toxic effects and its respective remedy are explained in detail. The scientific studies conducted on these compounds show the rationale of all these methods which are discussed here.

Table 1: Classification and selection criteria/ Graahya lakshanas

DRUG	CLASSIFICATION	LAKSHANAS
Haratala[1]	**PATRA HARATALA**	Golden Coloured, Snigdha, Guru, Bhasuram, Sukshma Patra, Rasayana Properties, Tridoshaghna And Kusthaghna
	Pinda Haratala	Small Lumps, Without Lusture, Stone Like Form, Low Weight, Not Good In Appearance.

	Godanti Haratala	Soft & Heavy, Without Lusture, Appearance Like That Of A Cow's Teeth, Has Yellow Blue Streaks At The Center
	Tabaki/Baghdadi Haratala	Highly Poisonous, Very Much Smooth In Touch, Possesses The Layers And Marked Weight And Is Known As King's Yellow
	Vakradala Haratala	It Has Layers, Heavy And Can Cure Leucoderma And Leprosy And Appears To Be A Special Variety, Which Has Been Used To Cure Indra Kustha
Manashila[2]	Shyamangi : Reddish white with blackish tint and heavy Kanaveeraka: Copper colour with certain brightness **KHANDHAKYA** : Bright coloured, heavy and easily powdered	
Gouripashana[3]	**SPHATIKABHAMALLA** is white in colour, of best variety ShankabhaMalla is creamish/yellowish white colour of better variety HaridrabhaMalla is yellow and of good quality	
	Sweta: resembles Shankha, white colour, it is krutrima **Peeta:** yellow coloured, naturally available, resembling colour of Dadima phala twak	

Table 2: Showing the general properties of Arsenic compounds

DRUG	RASA	GUNA	VEERYA	VIPAKA	KARMA	INDICATIONS	DOSAGE
Haratala[4]	Katu Tikta	Snigdha	Ushna	Katu	Kapha Vata Hara,Deepana,Bhutagna	Kusta,Katigraha,Visarpa,Arshas,Apasmara,Phiranga,Swasa	1/4th- ½ ratti 30- 60mg
Manashila[5]	Katu Tikta	Snigdha	Ushna	Katu	Kapha vata hara,Bhutagna	Kasa,Swasa,Agnimandya,Kandu,Jwara	1/32 – 1/16th ratti 3.75-7.5mg
Gouripashana[6]	Katu Tikta	Snigdha	Ushna	Katu	Kapha vata hara	Swasa,Twak Vikara,Slipada,Phiranga,Santapa,Sthoulya,Pandu	1/120th – 1/30th ratti 3 – 4 mg

Table 3: Showing chemical properties of Arsenicals[4,5,6]

PROPERTIES	HARATALA	MANASHILA	GOURIPASHANA
Molecular formula	As_2S_3	As_2S^2	As_2O_3
Molecular mass	246.0	246.0	197.0
Appearance	Orange crystals	Orange red	White

Melting point	310	320	312
Boiling point	707	565	465
Specific gravity	3.4 – 3.5	3.5	5.6 – 5.7
Hardness	1.5 – 2	1.5 – 2	3-4

SHODHANA OF TALA VARGA

The unprocessed Arsenic compounds produce various toxic effects and diseases. Henceforth the purification procedures are mandatory. According to Desha, Kala, Rogi Bala, Dosha etc Matra/ dosage is decided and given. Mostly procedures such as Bhavana, Swedana, Pachana using different media are employed in purifying these compounds.

Effect of Shodhana on Arsenicals:

1: Reduction in Particle Size: Example: Shodhana of Manashila by Bhavana[7]: Particle size of Ashuddha Manashila was 54.18µm while that of Ardraka swarasa Shodhita Manashila was 15.55µm which indicates that after Shodhana there was significant reduction in size if the particle.

2: Impregnation of Properties of Media to the material which lead to unique and suitable physicochemical changes. Ex: Shuddha Manahshila (ZM, SM, LEM, and LIM) showed significant anti-inflammatory activity at all three dose levels in a dose-dependent manner as compared with control. The Shodhita Manahshila is also found safe for medicinal use. In the earlier report, it was found that all the Shodhana media was found anti-inflammatory property by inhibiting prostaglandin and leukotriene biosynthesis to the elimination of 5-lipoxygenase or prostaglandin synthetase. The lavish production of pro-inflammatory cytokines (NO, IL-1, TNF-α, and IL-8) were also inhibited by these constituent. In another study, it was also showed that the extract of ginger juice decreased the elevated character of NFκB and TNF-α[8]

3: Induction of trace elements from the media used. Ex: Shodhita manashila by agastya swarasa bhavana shows presence of trace elements like Iron, Silica, Potassium, Calcium, Zinc, Manganese, Copper, Chromium, Magnesium, Sulphur in varied quantities.

4: Organic encapsulation: organic components of the liquid media are transferred to the material to make it organo-metallic or organo-mineral compounds, which are favourable to the body.

5: Chelation: Phytochelatins are heavy metal-binding peptides that play an important role in detoxification of heavy metals by chelation. Ex: Ginger contains two important sulphur-based amino acids called cysteine and methionine which can act as phytochelatins and can render arsenic nontoxic in the Manahshila[9].

6: Methylation: Detoxifying Arsenic in the body through accelerated excretion. In the liver by the addition of a methyl group to the arsenic and transforms it into a nontoxic form which is then excreted EX: Manashila shodhana by Ardraka, Cysteine- methyl donor peptide[10]

7: Preservation of glutathione: Glutathione, a natural antioxidant recycling enzyme is an important detoxifying compound present in the blood, which combines with arsenic and excretes it via the bile. Ex: Ingestion of ginger reduces the fall in the amount of glutathione in the blood[11].

MARANA OF TALA VARGA:

The process of incineration is described for Haratala[12] and Somala[13]. By the process of

incineration, Arsenic trisulphide is converted to Arsenic oxide.

TOXICITY STUDIES:

1. Acute toxicity of Suddha Manashila showed no immediate and evident toxic signs and mortality within 24 hours and also after 14 days observation.Chronic toxicity study of all three samples doesn't show mortality or evident toxic signsThe histopathological reports of chronic toxicity showed mild changes only in liver and kidney cells which were non-specific and reversible.The haematological reports shown increase in RBCs, Hb, Haematocrit and platelets which indicates positive immuno response[14].

2. The median lethal dose of Shuddha Malla is 16.65mg where as that of Ashuddha Malla is 12.96mg which shows the variable dose significance due to Shodhana. The 5 times the dose(1.8mg), 10 (3.6mg), 20 times(7.2mg) , 30 times (10.8mg) , 35 times (12.6mg) of therapeutic dose (0.36mg) proves Shuddha Malla to be non-toxic in rat. The 40 times the dose of therapeutic dose i.e. about 14.4 mg of Shuddha Malla is toxic dose in rats. In the repeated therapeutic doses for 14 days Shuddha Malla is non-toxic whereas Ashuddha Malla proves to be toxic. In the 28 days repeated therapeutic dose Ashuddha Malla is highly toxic, though Shuddha Malla shows some of considerable differences in liver architecture, the regenerative changes proves it to be non-toxic. The therapeutic index of Shuddha Malla is 3.08 which prove Shuddha Malla as non-toxic. Shuddha Malla is a very safe non-toxic drug in the classically indicated dosage limits as per acute and Sub-acute repeated dose studies[15].

Toxicity and treatment: If the processing of arsenicals are not done properly / over dosing/ resulting in ill effects, antidotes have been explained to combat them.

Table 4: Showing toxicity symptoms and the respective antidotes

DRUG	SIGNS OF TOXICITY	TREATMENT
Haratala[16]	Diseases of Vata and Kapha Prameha, Santapa, Spota, Snayu Sankocha	Kushmanda swarasa+ madhu Jeeraka + sarkara 3 days
Manashila[17]	Ashmari, Murakrichra, Mandagni, Malabaddhata	Ksheera + Madhu 3 days
Gouripashana[18]	Marana	Godugdha + goghrta+ sarkara Karavella swarasa

Rationale of Antidotes[19]: In case of Haratala: Rasamanikya prepared with Haratala processed in Kushmanda Swarasa is proved to be safe in rats when administered at therapeutic and at five times therapeutic exposure dose levels. Safety may be achieved as Kushmanda [*Benincasa hispida* (Thunb.) Cogn.] Swarasa is an antidote for Haratala poisoning. Studies have shown that cucurmosin is an acti ve compound in Benincasa hispida (Thunb.) Cogn, a kind of riboso me-inactivating protein and has high rate of cell apoptosis.

Role of Anupana: Anupana are nothing but the substances which are supposed to be taken with or after the intake of medicines. Mostly madhu (honey), ghrta (ghee) or plain water are used. Some have been specifically told to particular diseases.

-For Ex: Shudda Haratala+ Vasa swarasa in Swasa, with Pancha tikta kashaya in Kusta. The rationale behind could be the Synergistic action that is drugs in combination have more potent effect on the body rather than the individual drug.

-Drugs with high lipid - water partition co-efficient, lipid solubility, low degree of ionization have greater absorption in GIT and form the basic criteria for entry in to the Blood Brain Barrier. Ex: Madhu,Ghrita

-Some drugs when combined with certain other chemicals agents, form chemical complexes which are slowly soluble in body fluids depending upon the pH of the environment. This slow dissolution rate provides a constant release of the drug for sustained action. This type of drug designing provides:

Prolonged duration of action – used in treating chronic ailments

Sustained drug action – of those having rapid rate of absorption and excretion.

Reduced frequency of administration - for drugs required in small doses.

Stable plasma concentration maintenance:

To have reduced potential for adverse effects and to aid in uniform absorption from GIT

ARSENIC CONTAINING FORMULATIONS:

There are 100s of formulations described in Rasashastra that contain Arsenic compounds. Few important formulations are listed high based on the criteria:

1) Easily available
2) Affordable
3) Supportive scientific studies
4) Used by physicians in day-day practice

Table 5: Showing therapeutic utility of Arsenic compounds and its formulations with supportive research activities conducted.

Sl NO	ARSENIC FORMULATIONS	UTILITY
1	Talakeshwara Ras	Anti microbial activity against Staphylococcus aureus and Pseudomonas aeruginosa[20]
2	Makaradhwaja	Geriatric cure[21]
3	Manashila	Sedative hypnotic activity[22]
4	Swasakuthara rasa	Highly significant results in relieving the symptoms of Tamaka Shwasa when administered with Tambula Patra swarasa in the dose of 125mg BD for 15 days Effective against three strains of Stah. Aureus[23]
5	Unmadagaja kesari rasa	Significant results in clinical trial conducted on Kaphaja unmada wsr to Depression[24]
6	Rasamanikya	Rasamanikya is safe at therapeutic dose levels when used judiciously along with specified adjuvants[25].
7	Vatakulantaka rasa	In combination with other medicines showed marked improvement in case of Utthana vatarakta wsr to Scleroderma after Shodhana[26].
8	Trailokyachintamani rasa	Trilokya Chintamani Rasa is found to be effective in in all the cases of the covid 19 ranging from mild to severe

		patients[27].
9	Nityanada rasa	Nityanada rasa is one of the Rasousahdhi used in the management of Arbuda. Nityanand Rasa having the therapeutic properties like lekhana, rasayana, which will help for inhibiting the growth of cancer cells, acts like a curative therapy, ingredients used will help as immunotherapy, non-toxic, harmless , used as rejuvenating , correction of metabolic defects, it may help in treating Arbuda[28].
10	Sameerapannaga rasa	Talastha SPR without Manashila and Galastha SPR with Manashila has shown significant results in relieving signs and symptoms of Tamaka Shwasa Marked improvement in the ischemia-induced neurobehavioral deficits by attenuating ischemia-induced neuroinflammatory response at both gene and protein levels in animal study using Sameerpannag Ras Mixture (SPR, Pravala Pishti, and Guduchi Satva in ratio of 1:2:4) A case of Bell's palsy was successfully treated with SPR with some adjuvant medicines Sameer Pannaga Rasa has also shown good results in patients with hemiplegia (Pakshawadha). It acts as a stimulant (Uttejaka) upon nerve centers of the central nervous system SPR is proved safe medicine on account of different toxicological studies and having large LD_{50}. SPR has been proved as a potent anti-inflammatory medicine[29].
11	Malla sindoora	MallaSindoor and ShringBhasmaadministered together were found very effective and safe in patient of allergic rhinitis with increased absolute eosinophil count[30].
12	Laxmivilas rasa	research work on clinical ground elaborates clinical efficacy of laxmivilas rasa in Dushta Parishyaya[31]

Rasamanikya / Talasindhura / Talakeshwara Rasa / Mallasindhura / Gandhaka Rasayana, Mahalaxmi Vilasa Rasa can be recommended orally according to the patients Dosha , Bala, and other parameters for antifungal activity in Mucormycosis[32]

ARSENIC COMPOUNDS - TOPICAL APPLICATION

SI NO	ARSENIC FORMULATIONS	UTILITY
1	Mahamarichyadi Taila	The relief in symptoms of Psoriasis provided by Shaman Yoga along with local application of Mahamarichyadi Taila proves safe and effective in the clinical management for Psoriasis[33]

2	Loma shaatana lepa	Both Harataladi and ShamibeejadiLepa are effective in the management of facial hirsutism due to either PCOS or idiopathic origin[34]
3	Switra Hara Lepa	Many applicatons containing arsenic compounds have shown good results in switra[35]

DISCUSSION

It is an agreed fact that heavy metals like Arsenic are toxic by nature itself, but are they toxic after processing? The toxicity studies carried out on Arsenic compounds as already explained above render these minerals into therapeutically potent form fit for consumption in the prescribed respective doses after processing them by Shodhana/Marana. The method of processing like Swedana, Mardana, Bhavana , the different media used in processing and the duration of processing as already seen have a combined effect in rendering these compounds non-toxic in the respective dosage. Shodhana helps in reduction of particle size of the drug thus aid in quick and better absorption. The transfer of therapeutic properties from media to drug thus we can expect a synergistic effect from the combination. The use of different herbal media has different effects like chelation, methylation by which deposition of Arsenic in the system is prevented. Though the process of Marana is explained for Haratala and Somala they are mostly used after Shodhana and usage in bhasma form is limited as of now.

Anupana also plays a very important role in synergistically enhancing the drug action and increase the target reaching ability and also combating the possible side effects. Acharyas have also foreseen the possible toxicity that could arise because of improper purification or administration and have enlisted the remedies there in.

With the various studies carried out it is henceforth proven that the classical parameters right from selection of the right drugs, to processing them by Shodhana, Marana, selection of suitable Anupana all these tools make arsenicals much safe for internal consumption.

Rasashastra texts have described large number of formulations containing Arsenic compounds which can be used effectively in diseases. However the compounds presently used by clinicians and those available in market are just countable. The scientific studies carried out on these formulations suggest their efficacy in acute and chronic conditions and the quick relief in symptoms when used judiciously. However there is a need to carry out research in this area to prove the efficacy of many other formulations containing Arsenic and other heavy metals to the scientific world.

CONCLUSION

Based on the available research data, it can be concluded that Arsenic compounds and formulations containing them can be safely used in different diseases. However proper processing of drugs and factors like Desha, Dosha, Kala, Prakruti, Vikruti, Linga should be considered before fixing the dose and duration of the drug. Negative publicity of heavy metal toxicity should not hinder the globalization of Ayurveda.

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