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Review Article

EVIDENCE BASED REALITY CHECKS ON SAFETY & EFFICACY OF HERBO-MINERAL/ METALLIC FORMULATIONS

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ABSTRACT
The progressive acceptance of Ayurveda and its medicines post-pandemic creates new beginnings. Ayurvedic medicines are ancient, and their resurgence is necessary. Earlier, it was believed that Ayurvedic medicines are safe for all. But past centuries, awareness regarding toxicities caused by them is well proliferated among populations. The Safety and efficacy related concerns of Ayurvedic herbo-mineral/metallic formulations need to be clarified for the globalization of Ayurveda. R&D in drug development, pharmacotherapeutics, pharmacovigilance sections need to be carried out. This article provides justifications on the safety and efficacy concerns through compiling research on various formulations.

INTRODUCTION
The overwhelming growth of Ayurveda across the globe and sudden inclination of populations toward Ayurvedic treatment after Covid pandemic and its miraculous effect in various lifestyle disorders. But this also infused a certain amount of fear and anxiety among the other medicine systems of the world leading to the biggest questions of the century- "Is the Ayurvedic medicines safe or toxic? Where is the evidence? The Ayurveda medicines cause heavy metal toxicities?" and so on. A drug, under any system of medicine, should and must, pass the tests of efficacy, safety, and quality. The Ayurvedic medicines have their own strength and limitations like every other system of medicine. The factors behind hindrance in their globalisation are- lack of evidence-based research, differences in philosophy, regulation and standardization, cultural and historical factors, lack of IPR and its alternative, quality control and quality assurance etc.

These can be resolved by working on the decoding manuscripts, R&D, regulations, and legislations so that the position of Ayurveda in a post pandemic world where people have realised that prevention is better than cure is just not a cliché but a mantra. Attempts to answer, some of these questions regarding the safety and efficacy of Ayurvedic medicines through evidence-based justifications to make it more transparent irrespective of any bias.

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MATERIAL AND METHOD
The related material was collected through published research articles from reputed journals which were searched through various online search engines as PubMed, Google Scholar, Springer, AYUSH research Portal and DHARA online etc.

Rasa Shastra- The Ayurvedic Pharmaco-therapeutics
The history of *Rasa shastra* began prior to the 3rd millennium BCE and continued till today. Metal and minerals are an integral part of Ayurvedic therapeutics and are being used since ages to provide desired therapeutics effects in specific disease conditions. Prior to internal administration, the metals and minerals are to be passed through a set of classical procedures like *Shodhana* (purification), *Bhavana* (levigation), *Marana* (incineration)etc. that make them bio-compatible, removes toxic potentials and impart the therapeutic efficacy. These processes create a least toxic compound from most toxic metallic form. The chemical and structural makeup completely differs from their compound state as their surface area increases enormously which enhances their target drug delivery in very lesser dose without causing much

toxic effects. It is clear from the long history of usage of metallic preparations that properly processed Ayurveda medicines do not produce any toxic potential under judicious administration. However, toxicity with Ayurvedic medicines may occur, if these medicines are improperly used and taken for a long time in chronic diseases as OTC products or prescribed by such doctors, who do not have ample information of these medicines. The herbo-mineral compositions that combine numerous herbs and metal in a precise ratio will provide an enhanced therapeutic impact while lowering toxicity. There are two mechanisms for synergism depending on the nature of the interaction (i.e., pharmacodynamics and pharmacokinetic). In terms of pharmacokinetic synergism, the ability of one herb to facilitate the absorption, distribution, metabolism, and elimination of another herb is highlighted. While pharmacodynamics synergism is when the active constituents of various drugs show synergistic effect through similar therapeutic activities are targeted by diverse mechanism of action. The herbo-mineral formulations have both plant and mineral based pharmacological agents which may exert synergistic, potentialize, agonistic, antagonistic actions by virtue of its associated diverse active principles themselves.[1]

Is herbo-mineral/metallic formulations safe and efficient?

This big serious question on Ayurvedic herbo-mineral/metallic medicines started causing very severe damage on the foundation of Ayurveda and on what extend this question is precise, that is more questionable. Inadequate pharmacovigilance and extensive self-medication have resulted in adverse effects for certain groups of population using these preparations, leading to unfavourable publicity for these formulations. To address the concerns identified by these formulations, long-term pharmacotherapeutic and toxicity investigations are required. Various factors can contribute to the toxicity caused by herbo-metallic drugs as chemical nature of the metal, route of administration, dosage, residence time within the body, pharmacokinetics and dynamics, bioavailability, metabolic transformations of the preparation, age, gender, physiology, nature and stage of disease, and diet etc. As the physical and chemical makeup of these organo-metallic compounds comprehend a whole new set of properties which are absent in their original forms. This can all be achieved through the numerous classical procedures as mentioned above. Lack of skilfulness and preciseness of these procedures will lead to generate more toxic (free metallic ions) forms. Heavy metal toxicity arises due to their tendency to create complexes with essential biological radicals such as sulphydryl, hydroxyl, carboxyl, amino, and imidazole. Toxic effects are caused by the inhibition of different enzymes. Therefore, properly manufactured metallic formulations are profound of organometallic forms which are non-toxic in nature. Drug-drug interactions that take place when these preparations are administered alongside other herbal medicines are another undiscovered aspect that may have an impact on their efficacy and toxicity[2]. Perhaps, this scenario occurs because of lack of R&D in novel drug development. Till date, there are several research works (Table 1) carried out by different organizations all over the world to check the safety and efficacy profile of various formulations to hold up or undermine Ayurveda.

Table1: Depicting Research along with concluding their works in the field of safety and efficacy of herbo-mineral formulations

S.NO.	Title of the article	Concluding notes
1.	Effect of *Puta* on in vitro anticancer activity of *Shataputi Abhrak Bhasma* on lung, leukemia and prostate cancer cell lines (Tamhankar et al.)[3]	• *Abhrak Bhasma* demonstrates directly proportional relation between number of *Puta* (quantum of heat) and its efficiency in in vitro anticancer activity on all three cell lines, with highly substantial effect on prostate cancer cell lines. • The solubility of *Abhrak Bhasma* after *Amritikarana* (Procedure through which remaining blemishes removed along with enhancing efficiency) decreases, limiting its anti-proliferative efficacy.
2.	Acute and subchronic toxicity study of *Tamra Bhasma* (incinerated copper) prepared with and without *Amritikarana* (Chaudhari et al.)[4]	• The findings demonstrate that at therapeutic dose levels (5.5mg/kg) and therapeutic equivalent dose (TED) x 5 (27.5mg/kg), neither *Tamra Bhasma* sample produced any signs or symptoms of toxicity, however at higher doses of TED x 10 (55mg/kg) both samples produced signs and symptoms of toxicity. On repeated dosing for 28 days, *Tamra Bhasma* causes minor toxicity in the liver, kidney, heart, and thymus.
3.	Preparation and physicochemical	• The alkaloidal extract of Aconitum ferrox was evaluated using

	characterization of ingredients of Indian traditional medicine, *Mahamrutyunjaya Rasa* (Rai et al.)[5]	FTIR (Fourier transform infrared spectroscopy) and HPTLC (High Performance thin Layer chromatography) which implies the transformation of the alkaloid Aconitine (LD50- 0.08mg/kg) to Benzoylaconine (LD50- 24mg/kg), thereby enhancing its safety. • XRD (X-ray diffraction) and DSC (Differential Scanning Calorimeter) investigation of *Gandhaka* (Sulphur) revealed that purification (*Shodhan*) resulted in the conversion of orthorhombic sulphur into monoclinic sulphur, which then reversed to its initial form with greater purity. • Organic compound treatments produced *Gandhaka* and *Hingula* analogous to bodily tissues. Purified *Tankana* analysis revealed that the procedure resulted in water loss and a minor alteration in crystalline structure, with the endothermic peak shifting from 110.6°C to 104.2°C.
4.	Mercury-based traditional herbo-metallic preparations: a toxicological perspective (Kamath et al.)[6]	• The excretion of "*Makaradhwaja*," an Ayurvedic compound formulation containing mercuric sulphide, revealed no levels of mercury in urine samples collected from healthy individuals. • At a high dose of 1g/kg, the study shows both cinnabar and mercuric sulphide elicited vestibular ocular reflex system's dysfunction and disrupted motor performance in guinea pigs and caused aberrant auditory brain stem response in mice. The results showed that MeHg (Methyl mercury) and cinnabar suppressed Na+/K+ ATPase activity in the cerebral cortex irreversibly, whereas HgS inhibited Na+/K+ ATPase activity reversibly. This implies that insoluble HgS and cinnabar can be absorbed from the GI tract and transported to the brain. • After administering cinnabar to rats for 2 to 10 weeks at a dose of 10mg/kg/day, the auditory brain stem response (ABR) was examined for its ototoxic effects. A clinical dose of 10mg/kg/day generated ototoxicity following long-term exposure. Na+/K+ ATPase activity was changed, lipid peroxidation increased, and nitric oxide levels decreased. • The herbal formulation containing HgS was tested on Swiss albino mice, and the results revealed no negative effects even at doses 5–10 times greater than the standard dose (20–40mg/100 g) of mice. • *Kajjali bhasma* (mostly meta-cinnabar) did not cause any instances of genotoxicity in terms of micronuclei induction or DNA damage in animals treated with it, reiterating its safety despite its trace mercury level. • Mercury salts are taken up by the kidneys by two different pathways: first, via luminal membranes in proximal tubules forming cysteine S-conjugates (Cys-S-Hg-S-Cys), and second, by basolateral membrane through organic anion transporters. Inorganic mercury cannot cross the blood-brain barrier or the placenta, although a little amount of it that is ingested can be reduced in tissues and exhaled as mercury vapour. Also, it has been shown that a sizeable amount of mercury vapour may pass the blood-brain barrier. • Cinnabar is said to be distributed throughout the brain after being taken orally, with the cerebral cortex and cerebellum receiving the majority of the drug.
5.	Ayurvedic metal nanoparticles could be novel antiviral agents against SARS-CoV-2 (Sarkar et al.)[7]	• *Swarna Bhasma* has the potential to interfere with the spike protein and damage the coronavirus's outer coats. It has immunostimulant properties on macrophages and enhances phagocytic activity. It is an anti-inflammatory medication that

		boosts both cellular and humoral immune responses while lowering cytokine production. Vascular permeability and vasodilatation are encouraged by its capacity to affect T-cell activation. • The growth of novel corona viruses can be inhibited by *Rajata Bhasma*. • *Tamra Bhasma* may inhibit the replication of SARS CoV-2 by destroying the capsid protein. • *Yashada Bhasma* displays regulation of immunological response mediated by T cells. • *Swarna Bhasma, Rajata Bhasma, Tamra Bhasma*, and *Yashada Bhasma* are Ayurvedic metal nanoparticles that have the capacity to lower plasma interleukins, interferons, and TNF levels.
6.	Safety profile of Ayurveda *Rasoushadhi*: An appraisal of technical reports on quality and safety of selected *Rasakalpa*-Metal and mineral-based Ayurvedic formulations (Mahajon et al.)[8]	• Throughout the 90-day experiment, no death or significant indications of toxicity were seen in either the control or drug-treated groups of animals. • No aberrant findings were found during the gross pathological evaluation. Examining tissue slices stained with hematoxylin and eosin and fixed in paraffin has been the gold standard for pathology evaluation in toxicity investigations. The results of the investigations show a negligible build-up of metals in various tissues of the test-drug-treated animals, and their percentage was within acceptable limits.
7.	Safety evaluation of mercury based *Ayurvedic* formulation (*Sidh Makardhwaj*) on brain cerebrum, liver & kidney in rats. (Kumar et al.)[9]	• In comparison to control, the doses of SM (*Sidh Makardhwaj*) did not significantly alter neurobehavioral parameters, brain cerebrum AChE activity, liver (ALT, AST, ALP bilirubin), or kidney (serum urea and creatinine) function tests. • MDA (malondialdehyde) and GSH (glutathione) levels in these tissues did not alter significantly at dosages of 10 and 50mg/kg (Low and mid-dose respectively). Even there was no histological alteration in the cytoarchitecture of brain cerebrum, liver, or kidney tissues at above respective doses.
8.	*Mahayograj Guggulu*: Heavy metal estimation and safety studies (Lavekar et al.)[10]	• No group under study showed any apparent behavioural changes. Neither does it seriously disrupt physiological functions or harm any organs. • Measurements of the heavy metal concentration revealed levels of lead at 25.8g/g, mercury at 0.07g/g, and arsenic at 5.19g/g. The levels of lead alone are greater than those recommended by WHO. The other values are within the specified ranges. • The only factors that could be reason for worry are the somewhat elevated ALP activity, the mild declines in the total WBC and lymphocyte count, and the propensity for a declining platelet count, all of which point to myelosuppression.
9.	Safety and toxicity profile of some metallic preparations of Ayurveda (Prajapati et al.)[11]	• It was studied that at higher dose, *Tamra Bhasma* causes toxicity. The toxic effects seen were of moderate strength. These harmful effects may not occur at the therapeutic equivalent dose, which is five times lower than the administered dose. • There was no significant toxicity in the *Lauha Bhasma*-treated group. The hepatic cytoarchitecture and functions were only mildly compromised. • The epithelial growth may be a sign of androgenic activity and not be regarded as a pathogenic development, and the changes in kidney function are of mild severity and are probably reversible. Overall, *Yashada Bhasma* has no significant adverse effects on

		physiological functioning.
10.	Evaluation of neuro-protective activity of *Brihatvata Chinthamani Rasa* (Goshan et al.)[12]	• The test drug administration significantly increased catalase and decreased lipid peroxidation in comparison to the control group. • In contrast to the test drug, which showed normal cytoarchitecture, histopathological analysis of the hypothalamus in control rats indicated reduced cellularity and a preponderance of immature neurons in the granular layer. • In conclusion, the test medication maintained the usual cellular integrity of several brain areas while also possessing antioxidant storage capacity.
11.	Acute oral toxicity of *Madhumalini Vasant, Arshakuthar rasa* & *Sarvatobhadra vati*, an Ayurvedic herbo-mineral formulations in wistar rats (Waghmare et al.)[13]	• At a high dose of 2000mg/kg, the female wistar rats did not exhibit any signs or symptoms of treatment-related toxicity. During the 14-day monitoring period, no deaths were detected. • The results of this study showed that all three Ayurveda formulations are safer when taken at larger doses. It may be concluded that the LD50 exceeds 2000mg/kg (LD50> 2000mg/kg).
12.	Anti-tussive activity of *Shwasakuthara Rasa* a herbo-mineral formulation prepared with and without *Kajjali* (black sulphide of mercury) in SO_2 induced cough in Swiss albino mice. (Bhagyalakshmi et al.)[14]	• SKR1 (*Shwasakuthara Rasa* with *Kajjali*) and SKR2 (*Shwasakuthara Rasa* without *Kajjali*) reduced cough reflex by 70% and 56% respectively. • In comparison to inorganic mercury such as mercury sulphides, organic mercury like methyl mercury and ethyl mercury is determined to be 5000 times more toxic. From inorganic mercury, only a little quantity is absorbed. • Coughing can be prevented centrally and peripherally, respectively. Centrally acting medicines function by blocking the cough centre in the brain, raising the cough threshold whereas, peripherally acting agents either anaesthetize or demulcent the local nerve endings. Some of the constituents, such as *Kajjali, Manahshila, and Pippali*, may function centrally, while others, such as *Maricha, Shunthi, Pippali, Vatsanabha*, and *Tankana*, may work locally in lowering inflammation and modulating the cough reflex in albino mice exposed to sulphur dioxide.

Safety Aspects of Mercury Profound Formulations

Mercury is the foundational stone of Ayurvedic pharmaceutics (*Rasa Shastra*) which is quiet well known to the world for its highly toxic nature. It is highly urged by United Nations (UN) through Minamata convention (2013), "Mercury-Time to act" to ban on mercury trade due to its life-threatening disastrous effects. However, in the recent years, the use of mercurial preparations in Ayurveda has raised concerns and debate in the world due to the so far registered heavy metal toxicities and related ADR's. The state of mercury in which it is used in Ayurvedic formulations is mainly mercuric sulphide (Inorganic mercury) which is least toxic as it is insoluble and cannot be absorbed by blood circulation, it is unlikely to have any therapeutic effects since it may not even interact with cell receptors. Nevertheless, the inclusion of herbal substances in these formulations (Having mercuric sulphide) may change the therapeutic effects as well as the profile of cell absorption, distribution, and excretion. Cinnabar is the major source of mercury sulphide. It was studied that human gut flora can transform cinnabar into mercuric polysulfides rather than methyl mercury. More than 96% of cinnabar is composed of α-HgS, making it impossible for micro-organisms in the stomach to methylate the substance. Since HgS is so weakly soluble that it hardly ever releases mercury ions into water. Several purifying media are mentioned in ancient treatises to make mercury in its least toxic and more potent state. Use of CaCO3 as a purification media for mercury is still not properly understood. Most likely that metallic salts such as lead or tin, which are typically linked with mercury, will be eliminated as slags during the reaction with limestone. Other purifying agent is Garlic, which has been used as an antidote to mercury poisoning since long duration. Whereas glutathione, an antioxidant present in garlic, can eliminate mercury poisons from the body. Mercury binds to the sulphydrl groups in garlic and is eliminated from the body. Garlic includes allicin, ajoene, S-allyl cysteine, bioactive selenium, and other compounds that can help to

reduce not just heavy metal toxicity but also the oxidative stress caused by arsenic and other metals. These are some of the justifications behind the specific media and their importance in respective of declining mercurial toxicity and evaluating its medicinal worth in Ayurvedic sciences[15].

DISCUSSION

The Government of India is promoting Ayurveda on international level for its globalisation. Ayurvedic medicines already mark a milestone by presenting very well during COVID pandemic. These medicines are time tested and only require R&D in their safety and efficacy aspects. Ancient treatises of Ayurveda had shown how splendidly these medicines act on body and cures various diseases such as- *Chywanprash* as "*Parmukto Rasayanam*" (best rejuvenator)[16], *Chandraprabha Vati* as "*Sarvaroga Pranashini*" (eradicate all diseases)[17], *Yogendra Ras* as "*Sarvaroga kulantkrat*" (end all diseases)[18], *Yogaraj Gugglu* as "*Yogoayam amritopam*" (elixir like medicine)[19]. What makes these formulations exceptional besides having metals, minerals, herbs in them. Each and every ingredient of formulations are well researched, they are mixed with other ingredients in such ratio that they either enhance the cumulative properties of formulation or act as antagonist to suppress hyperactivity of some ingredients example- *Tankan* (borax) act as antagonist for *Vatsnabh* (Aconitum ferrox) while *Marich* (*Piper nigrum*), *Trikatu* (*Zingiber officinalis*, *Piper nigrum* and *Piper longum*), purified *Manhshila* (As2S2), and *Kajjali* (purified mercury and sulphur) act in synergistic way as mentioned under *Shwas Kuthar rasa*[20]. Metal and minerals in these formulations, went through numerous procedures which convert them in very finer state (nanoscale) which makes them *Yogavahi* (nano carriers) and *Rasayan* (immuno-modulator); preparing organo-metallic compound enhances their biocompatibility, specific site action, combating heavy metal toxicities. Everything is well documented in ancient texts regarding pros and cons of Ayurvedic metallic formulations usage, we just need to decode and rectify them along with it, R&D in reverse pharmacology, pharmacokinetics, pharmacovigilance, and drug development should be worked on. The whole debate and discussion on safety and efficacy can be resolved efficiently through above check points. Ayurvedic medicines are ancient, and their resurgence is necessary because it's now or never.

At the global level, Ayurvedic herbo-mineral/metallic formulations are at high risk. Western countries are restricting their import and export in the name of "Heavy metal toxicity". There are numerous international laws that are restricting the use of Mercury as a medicine such as Mercury export ban act 2008, Minamata convention on mercury, UNEP Global mercury partnership etc[21].

CONCLUSION

This is well established that impurified, organic mercury and other metal/mineral cause hazardous situations, but this statement should also be re-established that these can also treat n^{th} number of diseases in their purified state. As, above research compilation depict, Safety and efficacy of Ayurvedic formulations are directly dependent majorly on their SOP's (Standard Operating Procedures).

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