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AYURVEDIC NANOMEDICINE: BRIDGING ANCIENT AND MODERN SCIENCE

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Abstract

Rasashastra (Iatrochemistry) and nanomedicine share several conceptual similarities, though their applications differ. The classical objective of *Rasashastra* was not only treatment of diseases but also transmutation of base metals like Iron, Zinc etc into higher, noble metals like Gold (no longer practiced). Presently, with the advent of technology, the metals have been converted into nanoparticles using physical and chemical methods which are not eco-friendly. To address this limitation, sustainable and eco-friendly biological methods of employing fungus, bacteria, yeast and plant extracts have recently gained prominence. Among these, the plant extract-mediated synthesis known as green synthesis closely parallels the Ayurvedic process of *Bhasmeekarana.* Nanomedicine like *Rasashastra* is intended for therapeutic purposes, and also as a drug delivery agent, for diagnosis, control release, nano sensors, tissue engineering and stem cell manipulation. This article attempts to compare the traditional Ayurvedic techniques and contemporary methods for the synthesis of Nanomedicine. A comprehensive literature review was undertaken on classical

treatises such as *Rasaratna Samuchchaya, Rasa Tarangini, Ayurveda prakasha* to collate all the information on *Bhasma* (Nanoparticle) alongside scientific literature from databases including PubMed, Google scholar, AYUSH research Portal and ResearchGate were explored to compile information on research articles related to *Bhasma* and Green synthesis approach in nanomedicine. Although the concept remained same, there were variations in the preparation methods and philosophical foundations. The convergence of ancient innovation and cutting-edge technology can result in amelioration of the present healthcare setup.

Keywords: Ayurveda technique; *Bhasmeekarana*; Green synthesis; Nanomedicine; *Rasashastra*

Introduction

In a rapidly advancing era of healthcare, nanomedicine is emerging as a remarkable innovation. Notably, the principle of nanotechnology is seen rooted in ancient Indian medical system especially in the branch called “Rasashastra” which deals with pharmaceutical preparations derived from minerals, ores and metals. Bhasmas, which are the nano structural form of medicine, is utilized for treatment of various diseases for centuries. In the recent era, modern health care is revisiting these formulations in a different name and by making use of different technology to develop a similar dosage form. It has been used in various aspects of healthcare like treatment, drug delivery, enhanced solubility, bioavailability and efficacy. This marks the confluence of the emergence of the terminology “Ayurvedic nanomedicine” where the classical methodology of preparation of *can* be integrated with cutting-edge technology.

A brief about the history of *Rasashastra* and nanomedicine

Rasashastra is a branch of Ayurveda which deals with manufacturing medicines from minerals, ores, metals and herbs. It also deals with synthesis of *Bhasma, a* nano sized medicine through complex procedures like purification, levigation and incineration. This nano sized potential compounds are integrated with the potency of the drugs utilized during its production providing synergistic, target based, cellular level therapeutic effect.

Additionally, almost all *Bhasmas* possess *Rasayana* (adaptogenic and rejuvenating) properties, making them potent immunomodulators. References to mineral use appear as early as the Vedic period but the real boom came in the 15th–16th century during the iatrochemical revolution. The legendary alchemist Nagarjuna is credited with its evolution who proclaimed:

"***Sidhe Rase Karishyaami Nirdaridryamidam Jagat*** [1]" which means I will discover medicines from mercury and other naturally occurring substances to eliminate poverty from the world. *Rasashastra* mainly has two streams: 1) *Loha vada* - Alchemy focused on turning base metals into gold. 2) *Dhatu Vada* – Use of metals for therapeutic purposes.

Nano comes from a Greek word which means 'dwarf' or something very minute and depicts thousand millionth of a meter (10^{-9} m). Nanoscience is the study of the structure and molecules in the scale of nanometers ranging between 1 to 100 nm. Nanoparticles in terms of medicinal one appeared only in 1970s. Nanomedicine is defined by the European Science Foundation's forward Look Nanomedicine as: "Nanomedicine uses nano-sized tools for the diagnosis, prevention and treatment of disease and to gain increased understanding of the complex underlying patho-physiology of disease. The ultimate goal is to improve quality of life [2].

Both Ayurveda *Bhasma* and nano medicine share similar advantages in terms of nano-size, high surface area, quantum level effects and targeted delivery. However, there is difference in their preparation methods and philosophical foundations which will be dealt with in this article.

Methods

This review article synthesis information from Ayurvedic treatises like *Rasaratna samuchchaya, Rasaatarangini, Ayurveda Prakasha* which are the paramount treatises for *Rasoushadhis* used in Ayurveda. The sources of raw materials, plants used in the process of *Bhasmeekarana* (process of reducing to nanoparticle) and the traditional analytical techniques followed for the final products were documented. Simultaneously, different search engines like Google scholar, PubMed, AYUSH Research Portal, and Research Gate were scrutinized for articles on green synthesis of nanomedicine and research on

standardization of Ayurvedic nanoparticles were compiled from around 38 research articles. However, in this article 33 papers are considered and comparison between the traditional and contemporary techniques are made.

Source and classification of drugs used in *Rasashastra*

Natural occurring substances can be divided into 6 types namely:1) *Maharasa* 2) *Uparasa* 3) *Sadharana rasa* 4) *Ratna* (precious stones) 5) *Uparatna* (semi-precious stones) 6) *Lauha* (Metals) (Table-1). These are classified based on their varying magnitude of therapeutic potency and their capability in the mercury processing. Many of these drugs are considered under schedule E-1 of Drugs and Cosmetics Rules, 1945 which focuses on substances to be given with precaution and sold only under medical supervision.

Table 1 -Depicts classification of naturally occurring substances used in *Rasashastra*

Sl No	***Maharasa***	***Uparasa***	***Sadharana rasa***	***Dhatu-Upadhatu***	***Ratna-Uparatana***	***Sudha-Sikata***
1.	*Abhraka* (Mica)	*Gandhaka* (Sulphur)	*Kampillaka (Mallotus phillipinensis)*	*Swarna* (Gold)	*Manikya* (Ruby)	*Sudha* (Lime)
2.	*Vaikranta* (Tourmaline)	*Gairika* (Ochre)	*Gouripashana (White arsenic)*	*Rajata* (Silver)	*Mukta* (Pearl)	*Khatika (*Chalk)
3.	*Makshika* (Pyrite)	*Kaasisa* (Green vitriol)	*Navasadara (Ammonium salts)*	*Tamra* (Copper)	*Pravala* (Coral)	*Godanti (*Gypsum)
4.	*Vimala* (Iron pyrite)	*Sphatika* (Potash alum)	*Kaparda (Cowrie shells)*	*Lauha* (Iron)	*Marakata (*Emerald)	*Shwetanjana* (Calcite)
5.	*Shilajit* (Asphaltum)	*Haratala* (Orpiment)	*Agnijara (Ambargis)*	*Vanga* (tin)	*Pushparaga (*Topaz)	*Mrigashrunga (*Deer horn)
6.	*Sasyaka* (Blue vitriol)	*Manahshila* (Realgar)	*Girisindoora (Red oxide of mercury)*	*Naaga* (Lead)	*Hiraka (*Diamond)	*Shukti* (Pearl oytsre)
7.	*Chapala* (Bismuth)	*Anjana* (Collyrium)	*Hingula (Cinnabar)*	*Yashada* (Zinc)	*Neelam (*Sapphire)	*Shankha (*Conch shells*)*
8.	*Rasaka* (Zinc ore)	*Kankushta* (Ruhbarb)	*Mruddarashrunga (Litharge)*	*Pittala* (Brass*)*	*Gomeda (*Zircon)	*Shambuka* (Pila)

9.				*Kamsya* (White copper)	*Vaidurya* (Cat's eye)	*Samudraphena (*Cuttle fish bone)
10.				*Varta lauha* (Bronze)	*Suryakanta (*Sun stone*)*	*Kurma prishta (*Tortise bone)
11.					*Perojaka* (Turquoise)	*Kukkutanda twak* (Egg shell)
12.					*Sphatika* (quartz)	*Dugdha pashana (*Talc*)*
13.					*Vyomashma* (Jade)	*Kousheyashma* (Asbestos)
14.					*Trinakanta (*Amber)	*Nagapashana (*Serpentine)
15.						*Badarashma* (Silicate of lime)

Sources of nanomedicine

Ayurvedic *Bhasmas* and *Pishtis* (fine powder), prepared from various sources now correspond to engineered nanoparticles such as gold (AuNPs), silver (AgNPs), and iron oxide Nanoparticles used widely in biomedicine. Magnetite composed of Fe_3O_4 is encapsulated in basilicum seed mucilage (BSM) for sustained drug release which significantly increased the anti-bacterial activity [3]. Similarly, mineral based Ayurvedic ingredients like orpiment and red ochre are mirrored by synthetic mineral nanoparticles and nanoclays in modern applications. Various types of carriers are invented to deliver Arsenic trioxide used for carcinoma treatment [4]. Mineral drug nanoparticles play a significant role in tumor therapy by penetrating from the cell membranes to the tumor tissues [5]. Arsenic trioxide is one of the Aquatic sources such as conch shell and coral which are traditionally used in Ayurvedic preparations, find their modern counterparts in nano-calcium carbonate and hydroxyapatite, essential in bone and dental therapies. Gemstone based *Pishtis* like ruby and diamond are now represented by nanocrystalline versions with uses in drug delivery and biosensing.

Synthesis of Ayurvedic nanomedicine (*Bhasmeekarana* process)

The conversion of a raw metal or mineral into a very fine powder through incineration process is called *Bhasmeekarana.* The objective of this elaborate process is not only to enhance potency and efficacy but also to decrease their toxicity. It begins with the

appropriate selection of raw materials, subject them to *Shodhana* (purification specific for different materials) where metals, ores, minerals etc are heated at high temperatures and quenched in decoction of different plants repeatedly. It is then subjected to *Bhavana* which is the wet grinding of purified metals with plants which can create microscopic thermal cavities and allows the secondary plant metabolites to get activated and acts as chelating agents [6]. It then undergoes heating called *Puta* (heating in kilns of specific sizes and in a closed container for specific duration of time) [7]. For example, *Kukkuta puta* (traditional furnace of size 46cm × 46 cm × 46 cm is filled with cowdung cakes and a maximum temperature of 1000^0 C is attained for half an hour) and *Gajaputa* (pit size of 57 cm × 57cm ×57cm is filled with cowdung cakes and a maximum temperature of 1000^0 C is attained for 1 hour) [8]

Plant source for Ayurvedic nanomedicine

The different plant sources along with *Puta* used to prepare *Bhasma* are depicted in table-2 [9,10,11]

Table-2 Different plants and *Putas* used in *Bhasmeekarana*

Drug	**Plants or materials source for *Bhasmeekarana***
Abhraka (Mica)	Juice of *Kasamarda*
Makshika	*Gandhaka* + lemon juice
Kasisa (Pyrite)	*Kanji* (Fermented rice and urad dal)
Haratala (Orpiment)	Decoction of Peepal bark
Swarna (Gold)	Paste of R*asasindoora* with lemon juice is applied on the purified gold leaves
Rajata (Silver)	Paste of *Kajjali* (blended mercury and sulphur) with aloevera juice is applied on purified silver leaves
Tamra (Copper)	*Kajjali* and lemon juice paste applied on copper leaves
Lauha (Iron)	Decoction of *Triphala*
*Vanga (*Tin)	*Apamarga* (*Achyranthes aspera*) course powder

Naga (Lead)	Peepal bark powder *(Ficus religiosa),* K*anji*
*Yashada (*Zinc)	*Apamarga* (*Achyranthes aspera*) course powder
Pittala (Brass)	*Manashila* and G*andhaka* with lemon juice paste
Kamsya (white copper)	Paste of G*andhaka* and *Haratala* with lemon juice
Varta lauha (Bronze)	Paste of *Haratala* and *Gandhaka* with *Arka dugdha (Calotropis gigantea* milk)
Manikya (Ruby)	*Manahshila*, *Gandhaka*, *Haratala* with *Lakucha (Artocarpus lacucha*) juice
Mukta (Pearl)	Rose water
Pravala (Coral)	Aloevera juice
Marakata (Emerald)	*Gandhaka*, *Haratala*, *Manahsila* with *Lakucha* (Artocarpus lacucha) juice
Pushparaga (Topz)	Same as above
Heeraka (Diamond)	*Rasasindoora, Manashila, Gandhaka*
Neelam (Sapphire)	Same as above
Gomeda (Zircon)	Same as above
Vaidurya (Cat's eye)	Same as above
Godanti (Gypsum)	Aloevera juice
Mruga shringa (Deer horn)	Arka dugda *(Calotropis gigantea* milk)
Shankha (Conch shell)	Aloe vera juice
Shambuka (Pila)	Aloevera juice
Kurma prishta (Tortoise bone)	Aloevera juice
Kukkutanda twak Bhasma (Egg shell)	Same as above

Kousheyashma (Asbetsos)	Same as above
Badarashma (Silicate of lime)	Juice of *Mooli* (*Raphanus sativus*)

Synthesis and plant source in green synthesis of nanomedicine

Initially, generating nanoparticles (NP) was a combination of different disciplines like chemistry, engineering, physics and biology [12]. Metals like gold, silver and platinum were converted to NPs by a variety of chemical and physical techniques which were not eco-friendly [13]. For the same reason, several easy, safe, cost-effective, reproducible and scalable green synthesis approaches have been developed to produce NPs [6]. These involve employment of biological systems like fungus, yeast, bacteria and plant extracts for the synthesis of NPs [14]. Among these, plant extracts are the gold standard for green synthesis due to the availability of diverse plants and ease of use [6]. It is mainly based on redox process where the metal ions are reduced to crystallite clusters and then stabilized by the reactive phytochemicals [15]. It involves preparation of aqueous solution of metal salts and plant extract and then mixing both together [16]. The plant extracts from roots, leaves, flowers, fruits, stems and seeds are used and they also have the ability to produce NP with definite size, shape and composition [17].

Silver nanoparticles (AgNPs) are the easiest and least expensive to be able to produce using all the plants containing bio-molecules such as polysaccharides, vitamins, amino acids, proteins, phenolics, saponins, alkaloids, and/or terpene [18]. The rhizomes of *Acorus calamus,* whole plant of *Boerhaavia diffusa,* fruit of *Tribulus terrestris,* leaves of *Centella asiatica* gives a spherical shaped AgNP, leaves of *Eclipta prostrate* and *Nelumbo nucifera* gives a triangular AgNPs. Few other plants like *Datura metel, Carica papaya, Vitis vinifera, Vitex negundo, Calotropis procera* etc are also used [19].

Azadirachta indica, Medicago sativa, Aloe vera, Cinnamomum camphora, Pelargonium graveolens, Coriandrum sativum, Lemon grass *and Terminalia catappa* are few of the plant extracts which are used to produce gold nanoparticles (AuNPs) [20].

Plant extract from the leaves of *Eucalyptus sp*., *Thymus vulgaris* and *Gingko biloba Linn* are being used to produce Copper nanopartciles (CuNPs) [21]. Extracts from mango leaves [22], eucalyptus leaves, grape seed [23], pear tree leaves [24], vine leaves [25], *Terminalia chebula* fruit [26] are used for green synthesis of Iron nanoparticles (FeNPs).

Classical standardization of *Bhasma*

To ensure authenticity and quality of the formed *Bhasmas*, a series of traditional tests are performed (Table-3).

Table 3 -Traditional analysis of *Bhasma*

Ayurvedic Test	**Classical Description**	**Scientific Interpretation**
Varitaratva	Floats on water	Low density and very fine particle size
Rekhapurnatva	Enters the finger lines	Nano-size and good adhesiveness
Nischandratva	Lusterless	Signifies complete oxidation and transformation of raw metal into non-metallic oxides or salts
Nirdhuma	Does not emit smoke upon reheating	Complete combustion
Apunarbhava	Irreversibility to metallic form	Irreversible, stable, non-metallic compounds
Niruttha	Non-fusion with silver	Thermal stability and absence of free metal
Unnama	Floating with rice grain over Bhasma in water	Ultrafine particle size and low bulk density

Along with these general parameters, the color of the final product is unique to the parent drug. Table-4 represents the different colors for different *Bhasma*. With the advancements of Ayurveda research, different analytical techniques like Atomic absorption spectroscopy, inductively coupled plasma mass spectrometry (ICP-MS), x-ray diffraction (XRD), Scanning

electron microscope (SEM), Fourier transform infrared spectroscopy (FTIR), energy dispersion analysis of X-ray (EDAX), Raman spectroscopy, High performance liquid chromatography (HPLC) have been used to determine the quantitative, structural, chemical mapping, identification of compounds and also the size of the *Bhasmas* [27].

Table-4 -Color of different Bhasma

Metal	**Color**
Gold	*Champaka* (Reddish brown)
Silver	*Krishna* (Black)
Copper	*Krishna* (Black)
Brass	*Dhoosara* (Brown)
Lead	*Paaravata Prabha* (Greyish)
Tin	*Shwetha* (White)
Mica	*Ishtika varna* (Brick red)

Standardization techniques for green synthesis of nanomedicine

The characterization of green synthesis of nanoparticles includes the above along with ultraviolet -visible spectroscopy, attenuated total reflection (ATR), photoluminescence analysis (PL), dynamic light scattering (DLS), UV-visible diffuse reflectance spectroscopy (UV-DRS), transmission electron microscope (TEM), atomic force microscopy (AFM), field emission scanning electron microscope (FE-SEM), X-ray photoelectron microscopy (XPS), , thermal gravimetric differential thermal analysis (TG-DTA) or nuclear magnetic resonance (NMR) [28]

Pharmacological action of *Bhasma*

In clinical practice, the *Bhasmas* mentioned in Ayurvedic texts are either given as a 1) Single mineral/metallic drug along with synergistic adjuvant 2) Multi-mineral/ multi-metal /metallico-mineral compound 3) Herbo-mineral/ Herbo-metallic compound.

Few of the formulations available in the market are depicted in table-5 below [29]:

Table 5- *Bhasma* available in market with its dosage and actions

Compound	Ingredients	Dosage	Uses
Navrattan kalpamrit ras	*Pishti* of various *Ratnas* like *manikya*, *vaidurya pravala*, *rajavarta* etc, *Bhasma* of *Swarna*, *Rajata*, *Lauha*, *Yashada*, purified *Guggulu*, *Shilajitu*, *Guduchi*	62.5 mg	Carcinoma, anemia, complications of diabetes, respiratory disorders
Trailoakya Chintamani rasa	Diamond,gold, silver, Iron	62.5 mg	Severe respiratory tract infection, ovarian cyst, uterine fibroids
Swarna Vasanta malati rasa	Gold, *Piper nigrum*, *mukta* powder	62.5 mg	Tonsilitis, fever, bronchitis, decreased immunity, cancer, auto-immune disorders
Kamaduga rasa	*Gairika, Guduchi, abhraka bhasma*	250-500mg	Hyperacidity, headache, fever, blood pressure
Vasanta kusumakara rasa	*Swarna, Rajata, pravala bhasma*	62.5-125mg	Complications of diabetes, neuropathy, general weakness
Kumara kalyana rasa	*Bhasma* of *Swarna, abhraka, Lauha, Swarna makshika, rasa sindoora*	62.5-125 mg	General debility in children, fever, respiratory tract infections
Rasa raja rasa	*Rasa sindoora, Bhasma* of *Abhraka*, *Swarna, Rasa sindoora, Bhasma rajata, lauha, ania somnifera, Syzygium aromaticum*	62.5-125 mg	Paralysis, hemiplegia, rheumatism, insomnia, stroke

Shwasakutara rasa	Black sulphide of mercury, *Vatsanabha*, *Trikatu*	125-250 mg	Cough, pneumonia, bronchitis
Yogendra rasa	Red sulphide of mercury, *mandora*, *Abhraka*, *myristica fragrans*	62.5-125 mg	Paralysis, muscular weakness, insomnia, headache
Bolabahda rasa	Black sulphide of mercury, *Guduchi, Commiphora mukul*	125-250 mg	Bleeding
Pravala panchamruta	*Pravala, mukta, shankha* pishti	125-250 mg	Source of natural calcium, hyperacidity, burning sensation
Punarnava mandoora	*Mandoora, Boerhavia diffusa, Picrorhiza kurroa, Embelia ribes*	125-250 mg	Diuretic, anemia, swelling around joints, ascitis

Many of the Rasoushadhis, require Parada (Mercury) as a base either in the form of Kajjali (Blended combination of mercury and Sulphur) or Hingula/Cinnabar). Although mercury is a neurotoxin, the *Parada* used in Ayurvedic formulations in different forms is proven to be safe and free from toxicity on Zebra fish model [30]. Research has also established that cinnabar is not converted into methyl mercury in the human intestinal bacteria and thus proves it to be safe for human consumption [31].

The comprehensive information available in the Ayurvedic texts pertaining to standards of raw materials, standard operative procedures for different dosage forms, quality control aspects of in-process monitoring and for finished products, its shelf life, posology, duration of usage, safety, possible adverse reactions upon inappropriate usage of these medicines and their management, diet advises while on these medications infer the awareness of Good Collection Practices (GCPs), Good Manufacturing Practices (GMPs), Good Dispensing Practices (GDPs) etc mentioned in Ayurveda treatises [32].

There are several initiatives taken by the Ministry of Ayush to ensure the safety of the *Rasoushadhis* currently available in the market. One such effort was the retrospective compilation of a compendium of the OPD (Outpatient Department) data from past five years collected from 24 peripheral clinical institutes of Central Council for Research in Ayurvedic

Sciences (CCRAS) of the commonly prescribed *Rasoushadhis* for various diseases. It retrieved the records of around 1,09,307 OPD patients around 21 states/ Union Territories of India representing different geographical regions. Notably no Adverse Drug Reactions (ADRs) or Suspected Adverse Reactions (SAR) or any other untoward effect were reported during the treatment period or follow-up period. It is important to highlight that all the prescriptions were rooted in the classical Ayurveda approach of personalized treatment involving variations in dose, *anupana* (adjuvant) and co-medications [33].

Conclusion

The green synthesis of nanomedicine is an emerging field of medicine and is very similar to the Ayurvedic methodology of *Bhasmeekarana*. This shows that Ayurvedic wisdom and innovations stands relevant in modern healthcare and it can provide a more precise, personalized, safe and holistic treatment to the modern diseases. Even though there is difference in their applications and principles, integration of the traditional Ayurvedic wisdom with modern technology has the prospective to elevate healthcare to unprecedented levels**.**

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Conflict of interest

There is no conflict of interest between the authors.

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