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Letter to Editor

Revisiting the Ancient Claims of Nanomedicine

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Abbreviations

XPS: X-Ray Photoelectron Spectroscopy, ICP: Inductively Coupled Plasma, EDAX: Elemental Analysis with Energy Dispersive X-ray analysis, DLS: Dynamic Light Scattering, TEM: Transmission Electron Microscopy, PSD: Particle Size Distribution, FTIR: Fourier Transform Infrared Spectrometry, SEM: Scanning Electron Microscopy, XRD: X Ray Diffraction, AFM: Atomic Force Microscopy.

Sir,

Recent reports aptly introduced and mandated in-depth deliberation on the scope and applications of nanotechnology in medicine [1]. Metallic nanoparticles (monometallic/bimetallic) have been recognized to have wide range of interesting biomedical applications [2]. Some of the metal compounds are essential for functioning of specific human organ systems, and any imbalance in their levels may lead to with various illnesses. The role of metals in curing of ailments was first documented in ancient Ayurveda literature [3]. In the light of advent of engineered nanoparticles in therapeutics, which are high-cost, and rising awareness for their possible harmful effects, [4] it is sensed necessary to revisit comparatively safer, economical and most ancient application of nanomedicine- 'Ayurvedic *Bhasma*' (biogenic metallo-mineral nanoparticles) [5]. Present attempt shares and propose a new dimension of understanding of '*Bhasma*' in the emerging area of nanomedicine [6].

Elemental form of metals is not absorbable and may produce toxic effects [7]. *Bhasma* are unique herbo-mineral-metallic-compounds in the size of nano-dimensions (usually 2-50 nm) as established by modern microscopic and spectroscopic techniques [8]. *Bhasma* are products of ancient Indian alchemy, the 'Ayurveda Rasa Shastra,' used for treating diverse chronic ailments. The pharmaceutical *modus operandi* is called "*Bhasmikarana*" (making into ash/oxide), a systematic and step-wise procedure that involves purification followed by repeated, controlled and prolonged heating of metals/minerals with suitable ingredients (of organic liquid media). It converts original metal/minerals to oxide state, and removal of residual toxic molecules. In *Bhasmikarana*, metals are processed with herbs, and organo-metallic/organo-mineral complexes are formed (having improved stability and functionality), that help in assimilation and selective/targeted/controlled drug delivery into the human body. The process is also aimed to reduce the particle size and thus converting metals to *Bhasma* nanoparticles, which are biocompatible, bio-assimilable, absorbable and suitable form for the human body [4,6,9]. Hence, the use of *Bhasma* is nothing but ethno-nanomedicine since it is not only an ancient traditional medicine system but also uses nanoparticulate size of metals/minerals for therapeutics [6].

Bhasmikarana converts the metal from its zero valent state to a higher oxidation state form, and removes the toxic nature of metal and its oxide while rendering the metal oxide with high medicinal value [10]. It is distinct from the approaches used for manufacturing engineered nanoparticles [4]. Analysis of *Swarna Bhasma* (gold calx) by FTIR and XRD shows that pure Au in zero valency state [11].

Ancient classics have quoted certain tests for characterization of ideal *Bhasma*, namely, *Varna* (colour), *Varitara* (floats on water), *Unama* (floating of grain on *Bhasma* already floating on water), *Rekhapurnata* (fill furrows of finger tips when taken between thumb and index finger), *Slakshnatvam* (smooth), *Sukshamatva* (very fine), *Anjana Sannibha* (soft and smooth like collyrium), *Nishchandratvam* (lack of luster), *Gatarasatvam* (tasteless), *Avami* (do not produce nausea on administration), *Ketaki Rajah samah* (nano-sized as pollen grains of *Pandanus odoratissimus*), and *Apunarbhava/ Niruttha* (stays in non-metallic state) [12]. Likewise, modern analytical parameters are now developed to study the particle size of engineered metallic nanoparticles (e.g. PSD, SEM, XRD, TEM, EDAX); which are also adopted to investigate various Ayurvedic *Bhasma* (Table 1) [13-19].

All the engineered nanoparticles are not meant for human use the way *Bhasma* preparations were meant. *Bhasma* are biologically produced nanoparticles with quick and targeted action, act as multi-elemental cocktails, [8] and share some common attributes

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like *Rasayana* (immunomodulation and anti-aging quality), *Yogavahi* (target drug delivery), *Alpamatra* (prescribed in minute doses i.e. 5-250 mg/day), *Rasibhava* (readily absorbable, adaptable, assimilable), *Shigravyapi* (quickly spreads), *Agnideepana* (increases metabolism at cellular level and acts as catalyst) and *Kshipra arogyakaari* (quickly acts). *Swarna Bhasma* (size ~ 27 ± 3 nm) exerted antioxidant/restorative effects in ischaemia in albino rats, ameliorated symptoms of arthritis, ischaemia (stroke) and at 4 nm size helped in increased apoptosis in B-chronic lymphocytic leukemia [6,12] Few more clinical evidences of commonly used *Bhasma* are: *Mandura Bhasma* (iron calx): microcytic anemia and haemolytic jaundice; *Tamra Bhasma* (copper calx): hepatoprotective and antioxidant; *Yashada Bhasma* (zinc calx): myopia, diabetes and leucorrhea; *Mukta Shukti Bhasma* (pearl-oyster calx) (size ~ 22.52 ± 0.45 µm): acidity, inflammation, pyrexia, tuberculosis, cough, asthma, and increase the bone mineral density; *Shankha Bhasma* (conch shell calx): hyperchlorhydria, duodenal ulcer, sprue, colic and hepato-splenomegaly [12].

Historical evidences propose Ayurveda as pioneer in the pharmaceutical processing and safer therapeutic use of metals. Even the heavy metals (Hg, Pb) and toxic metals (Cu, Pb) are converted to relatively non-toxic form through the processes of *Bhasmikarana* [9]. The incidences of adverse effects of *Bhasma* therapy however are not so uncommon, though not documented scientifically, are assumed to be due to noncompliance to prescribed guidelines of 'Rasa Shastra' manufacturing. Thus *Bhasma* are biocompatible, non-toxic and non-antigenic in nature [3]. XANES- and EXAFS-based analysis of Hg-based nano-drug *Rasasindura*, carried out in Bhabha Atomic research centre, revealed composition of single-phase α-HgS nanoparticles (size~20 nm), free of Hg^0 or organic molecules, and better controlled structural parameters (size dispersion, coordination configuration) [20]. The non-existence of Hg^0 implies the absence of Hg-based toxicity, and the stable α-HgS form (strong Hg-S covalent bond) ensures the integrity of the drug during delivery and prevention of its reduction to Hg^0 within the human body. The work not only demonstrated the non-toxicity of *Rasasindura*, but also places the Ayurvedic synthesis method (*Kuipakwa* method of *Bhasmikarana*) on par with contemporary techniques of nanoparticle synthesis[20].

To sum up, since the benefits of nanomedicine prepared by the "traditional" Ayurveda routes are significant and undeniable, *Bhasma* may hold a strong relevance in therapeutics as the conventional counter part of engineered nanoparticles.

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Table 1: Detection of nanoparticles in Ayurvedic *Bhasma*

Metal/Mineral *Bhasma*	Nature of compound	Analysis	Finding (Nano-dimensions)	Ref.
Swarna Makshika Bhasma	$CuFeS_2$ calx	SEM	1-2 µm	[14]
Yashada Bhasma	Zinc calx	XPS, ICP, EDAX, DLS, TEM	*Bhasma* particles in oxygen deficient state and nano-sized	[15]
Lauha Bhasma	Iron calx	TEM	50-100 nm	[16]
Mukta Shukti Bhasma	Pearloyster calx	DLS	1.22-10.20 µm (6 percent were less than 50 nm)	[17]
		TEM	15-50 nm	
Swarna Bhasma	Gold calx	XRD	23-37 nm (Scherrer formula)	[18]
		TEM	Globular morphology, average particle size- 57 nm.	
		AFM	Globular morphology, average particle size- 56 nm.	
Vanga Bhasma	Tin calx	XRD	12-50 nm	[19]
Rasasindura	HgS compound	XRD, TEM, XPS, EDAX	20-50 nm	[20]

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