AYU

Access this article online
Website: www.ayujournal.org
DOI: 10.4103/0974-8520.153785
Quick Response Code:

Review Article

Engineered nanoparticles: Revisiting safety concerns in light of ethno medicine

Suhani Palkhiwala, Sonal R. Bakshi

Institute of Science, Nirma University, Ahmedabad, Gujarat, India

Abstract

The nanoparticles are a miracle invention of the century that has opened novel avenues of applications in various fields. The safety aspect of exposure to nanoparticles for humans, plants, animals, soil micro-flora, and ecosystem at large has been questioned. The safety concern can be addressed by laboratory studies to assess the actual risk and recommend exposure limits and related regulation. There is also a suggestion for considering the nanoparticle form of conventional compounds as a new chemical and subject it to safety assessment in line with the chemical regulatory agencies. In the light of the current scenario of popularity and safety concerns regarding nanoparticles, the use of ancient metal based forms like, *Bhasma* is revisited in the present article. The current approach of green synthesis of nanoparticles is compared with the Ayurveda *Rasayana Shastra* guidelines of *Bhasma* preparation and modern preparation of engineered nanoparticles. Since the benefits of nanotechnology are undeniable, and safety concerns are also not ungrounded, there is a pressing need to revisit the ways nanoparticles are manufactured, and to carry out safety assessment by the techniques specially adapted for this novel compound.

Key words: *Bhasma*, conventional nanoparticles, engineered nanoparticles, ethnomedicine, metal based Ayurvedic preparations, *Rasa Shastra*, regulatory guidelines, safety evaluation

Introduction

The invention of nanoparticles is not less than a miracle due to the unique properties that offer innovative and life-changing products and technologies in the fields of medicine, industries such as paint, food processing, fabric, information technology, etc., Nanotechnology is however also questioned in terms of safety for human, also animals, plants, and ecosystem at large. There has been exponential growth in this field with a wide variety of products, which are questioned for safety by many international organizations. Reports identified multiple scenarios through which humans could be exposed to engineered nanomaterials (ENM) including occupational, environmental, and consumer exposure.

Are nanoparticles safe? Agencies addressing safety assessment

Risk assessment task is based on the possibility of exposure and potential hazard to make regulatory decisions.[1] The likelihood of adverse health or environmental effects due to exposure to potentially hazardous chemicals for regulation is under the scope of government agencies and international organizations viz., the Environmental Protection Agency (US EPA), the European Chemical Agency, the Organization for Economic cooperation and Development (OECD), and the World Health Organization. These provisions for general chemicals have been found to be limited for safety evaluation of ENM. Gaps in basic information on hazard, exposure and dose–response can lead to ambiguous, largely qualitative risk estimations based on projected assumptions, which may fail to define appropriate risk management actions. Nevertheless, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks and the European Food Safety Authority have recently reviewed the available information and concluded that, despite the overwhelming uncertainties, the risk assessment framework is applicable to ENM if properly adapted to address their unique properties.[2]

A compound in nano form should be considered as a new compound

The properties that make nanoparticles unique and responsible for their importance in industrial and biomedical application also raise the safety concerns. The nano forms have unique properties in terms of magnetic, catalytic, optical, electrical, and mechanical attributes when compared to conventional, that is, non-nano or bulk forms.[3] These are increasingly preferred for use as fillers,

Address for correspondence: Dr. Sonal Rajiv Bakshi,
Institute of Science, Nirma University,
Ahmedabad, Gujarat, India.
E-mail: sonal.bakshi@nirmauni.ac.in

opacifiers, catalysts, water purification system components, semiconductors, cosmetics, microelectronics, etc., that are certainly likely to come into direct and indirect contact with humans. In the case of the biomedical field they are used, especially as drug-delivery agents, biosensors or imaging contrast agents through direct ingestion or injection into the body. The nanomaterials are often coated with biomolecules such as DNA, proteins, and monoclonal antibodies to target specific cells for imaging and drug-delivery uses. Metal oxides such as zinc oxide (ZnO) and titanium dioxide (TiO_2) in their nanoparticle forms have become a part of daily use. They appear on the ingredients list of common household products as diverse as cosmetics, sunscreens, toothpaste, food coloring, paint, and coatings for vitamin supplements. TiO_2 and ZnO are particularly valued for the high refractive index and bold white coloration making them widely used whitening agents. They are also common ingredients of sunscreen as they are able to block out both ultraviolet A and B lights.[4] Both TiO_2 and ZnO are the nanomaterials that are easily accessible to the human body. There are more chances of them penetrating the body through different means [Figure 1].

The considerable interest in developing these ENM is because their basic properties would be differing in fundamental and valuable ways from those of their bulk counterpart. However, regarding the regulatory approach, the Food and Drug Administration (FDA) guideline seems to allow using the ENM in foods as generally regarded as safe (GRAS). Thus marking of the product to have nanoparticles, is not mandatory. The ENM have been used to improve food quality during storage thus increasing the shelf life; however, uncertainties remain about how to determine the safety of using such food. FDA has reviewed the uncertainties that are associated with the safety aspect of use of ENM and decided that it need not have an additional arrangement to regulate products containing such materials. Instead, FDA encourages but does not make it mandatory for companies using ENM in the food, to consult with the agency regarding whether such substances might be GRAS. Since GRAS notification is voluntary, the companies do not essentially need to mention nanomaterials in their products, thus there seems to be no fool of proof way of knowing the extent to which ENM have entered the food supply. The regulatory guidelines are not similar globally. However, all food ingredients that incorporate ENM must be submitted to regulators in Canada and the European Union before they can be marketed.[5]

The government and nongovernment agencies like The International Centre for Technology Assessment, Centre for Food Safety, Friends of the Earth, and Institute for Agriculture and Trade Policy considered it to be of prime importance to put it before the regulatory bodies like FDA to consider nanoparticles as a new compound and not consider it safe as such because the native form is recognized as safe.[6] The National Toxics Network, Australia has reported that ZnO in the nano form shows the potential risk to humans.[7] On the other hand, TiO_2 bulk is classified as 2B by the International Agency for Research on Cancer, whereas nano form remains to be conclusively studied.[6]

Materials and Methods

A review of manufacturing methods and criteria for *Bhasma* prevailing in ethno medicine was carried out in order to compare with the same for engineered nanoparticles. The figures and table depict the comparative data. In present study, the details along with the concern for safety due to increased exposure to nano particles is described.

Bhasma, the metal compounds in nano dimensions: Conventional counter part of nanoparticles

In the light of this rising awareness for possible harmful effect of engineered nanoparticles, author think it is necessary

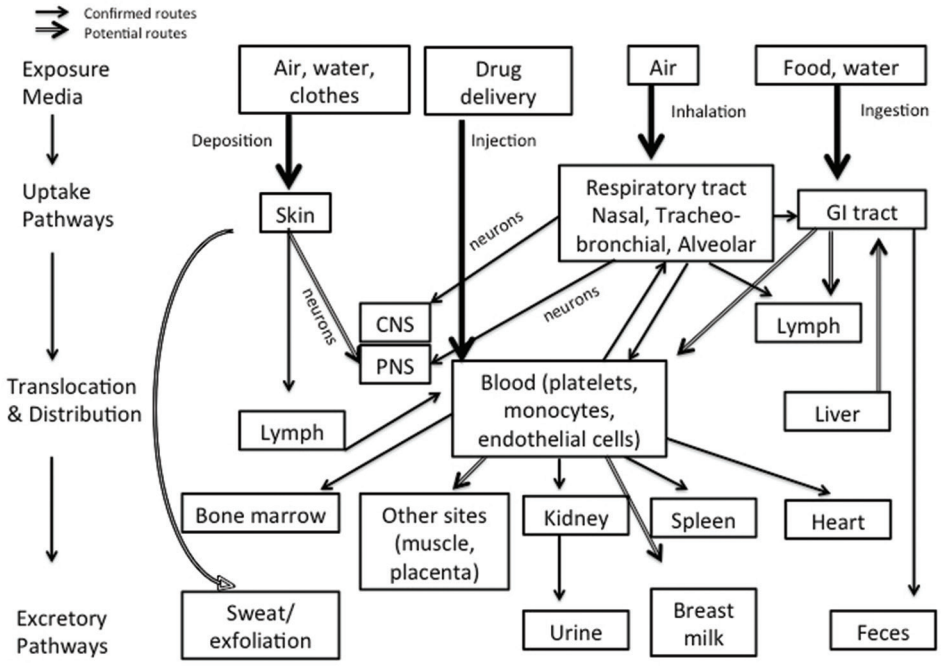

Figure 1: Entry routes of nanoparticles in the body

to revisit the ancient counterpart of nano that is used in traditional medicine that is, *Bhasma*.[8,9] The ethnomedicine branch "*Rasayana Shastra*" deals with *Bhasma* that are metal compounds in the size of nano dimensions.[8,10] *Bhasma* is the herbo-mineral metallic drug preparations unique to the Ayurveda, Unani, and Siddha systems of alternative or traditional medicines. These are prepared with herbal juices and used for treating diverse chronic ailments. These are considered products of classical alchemy; inorganic compounds of certain metals and present in a fine powdered form like oxides in gems. *Bhasma* literally meaning ash is a mineral preparation that is made from precious metals and their naturally occurring salts.[11] The manufacturing is called "*Bhasmikarana*" which means converting a compound into ashes. It is distinct from the approaches used for manufacturing engineered nanoparticles [Figure 2]. It is an elaborate process [Figures 3 and 4], which converts the metal into its specifically desired chemical compound eliminating the toxicity of the metal, making it compatible for human medicinal purpose.[12] The process helps converting the metal at zero valent state to a higher oxidation state, which is pivotal for reducing the toxicity of the compound thus rendering the metal oxide with high medicinal value.[13] Herbo-mineral formulations are very specific in terms of the organic media (juice or decoction of herbs), quantum of heat exposure during manufacturing by processes called *Shodhana* (means purification or potentiation) and *Marana* (means incineration). The metal mineral compounds in *Bhasma* form acquire many novel attributes, which may be due to the steps involved in the preparation as shown in Figures 3 and 4.

Some of the metal compounds are essential components of specific human body organ systems, and any imbalance in the amount is linked with various illnesses. The role of metals in curing of ailments was first realized in Ayurveda.[14] Zn for instance is present in blood, sensory tissues, and flesh. Imbalance in the Zn levels causes problems related to the nervous system such as despondency, anxiety, and dullness of intellect, extreme forgetfulness, and irritable temperament. Thus, the levels of exposure to metals need to be controlled for homeostasis.[12] *Jasada Bhasma*, which is a unique preparation of Zn, has been used in the treatment of diabetes and age related diseases. Nano sized gold particles are reported to be effective in amending symptoms of mycobacterial, collagen and pristine induced arthritis in rat models.[12]

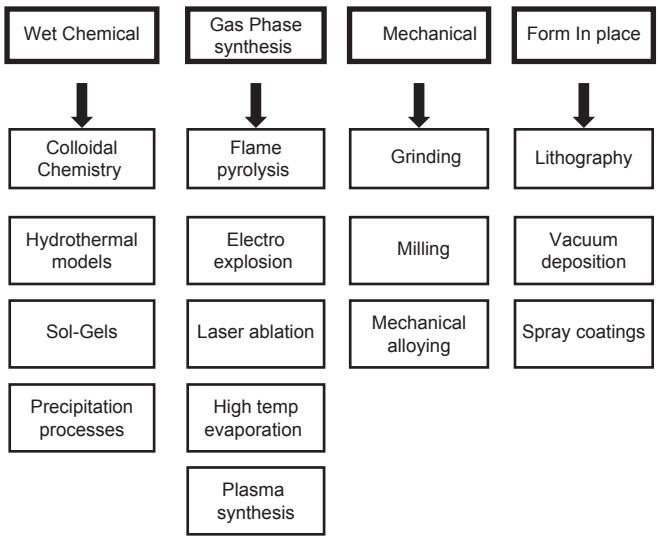

Figure 2: Methods to make nanoparticles

The allopathic medicines are widely used however; the traditional medicines are considered safer options in general. 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 "Ayurveda *Rasayana Shastra*" manufacturing [Table 1].[8,15,16] There are various physico-chemical characters that are ascertained by prescribed tests listed in the table. These tests are done to confirm the basic attribute of size, that is, "*Sukshmatva*" or fineness, which is demonstrated also by the electron microscopy, mass spectrometry, etc., laboratory techniques.[12] It can be assumed that it is a prerequisite for the preparations to fulfill these criteria in order to be safe and effective for human use. The Ayurvedic concepts of *Marana* (means trituration) and *Bhavana* (means levigation) are used to reduce the particle size. It has been reported that manufacturing methods of *Bhasma* are in tune with nanotechnology of modern era and *Bhasmas* are nearer to the nano crystalline materials, similar in physico-chemical properties except that *Bhasma* is prepared in the presence of various plant products like juices, concoctions, etc.[8,12] The engineered nanoparticles are found to be highly reactive due to the free electrons present on their surface, hence, these can be very sensitive to the environmental factors such as pH, temperature, electrolytes, and solvent, and have a tendency to aggregate. The use of plant extracts may provide capping of reactive nanoparticles and thus make *Bhasma* biocompatible, safe, and effective when manufacturing norms are properly followed. Considering environmental toxicity or biological hazards associated with chemical synthesis, green synthesis for nanoparticles is advocated, which can be considered as parallel of ancient *Bhasma* preparation in modern science. Green synthesis of nanoparticles involves use of natural polymers (gelatin, dextran, starch, chitosan) mainly of plant origin, which are used to make the nanoparticles more biocompatible and beneficial.[17,18] It is reported that, when nanoparticles are integrated with biological molecules their stability, functionality and effectiveness is improved due to the altered surface chemistry. The nanoparticle coating is found to be crucial for ensuring the bioavailability due to the surface chemistry that leads to formation of aggregates, which can limit the bioavailability.[19]

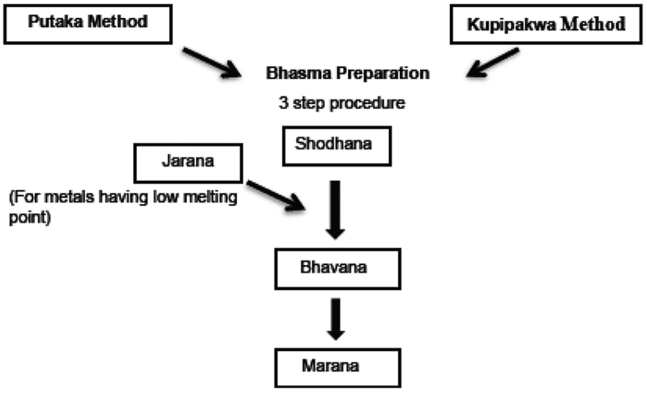

Figure 3: Preparation of *Bhasma*

Table 1: List and details of Ayurveda *Rasa Shastra* prescribed tests of a *Bhasma*

Sanskrit equivalent	Physical characteristic	Description
Visishta Varnotpatti	Specific colour	There is a specific colour for each *Bhasma*. If there is an alteration in the colour it is suggested that the *Bhasma* is not made properly, since a particular metallic compound is formed during *Bhasma* preparation and every chemical compound possesses a specific colour
Rekhapurantva	Fineness to enter finger ridges	*Bhasma* particles should be of minimum size so that it can be easily absorbed and assimilated in the body. It should be so fine that it should be able to fill the furrows of finger tips. A little amount of *Bhasma* is rubbed in between index finger and thumb to observe whether the particles can fill furrow of finger tips
Varitaratva	Lightness to float in water	The test is based on the law of surface tension. Little amount of *Bhasma* is taken in between index finger and thumb, after which it is sprinkled slowly on stagnant water surface from a short distance. If its properly incinerated, the *Bhasma* shall float on the water surface
Gatarastva	Tastelessness	Properly incinerated *Bhasma* of a metal should be of particular taste. It indicates transformation of particular metallic taste to compounds of specific taste
Nischandratva	Lustrelessness	The *Bhasma* must not be shiny before therapeutic application. Luster or shine is a character of a metal. After proper incineration the luster of the metal should not remain. Therefore, *Bhasma* is observed under bright sunlight, for assessing whether luster is present or not. If luster is present, it still needs further incineration
Anjanabhatva	Smoothness	*Anjana* (collyrium) is smooth in character and it doesn't create any irritation when applied. Properly incinerated *Bhasma* should be smooth and should not create any irritation to the mucous membrane of the gastrointestinal tract
Apunarbhavtva	Permanence	*Apunarbhavtva* means incapability to regain original metallic form. For this test *Bhasma* is mixed with equal quantity of *Mitra Panchaka* (seeds of *Abrus precatorius*, honey, ghee, borax and jiggery) and it is sealed in *Sarava Samputa* (earthen pots), thereafter similar grade of heat used for preparation of particular *Bhasma* is applied and on self-cooling product is observed
Niruthatva	Irreversibility	It is to test the inability to regain metallic form of metallic *Bhasma*. In this test *Bhasma* is mixed with a fixed weight of silver leaf, kept in earthen pots and similar grade of heat is applied and after self-cooling, weight of silver is taken. Increase in weight of silver indicates improperly prepared *Bhasma*

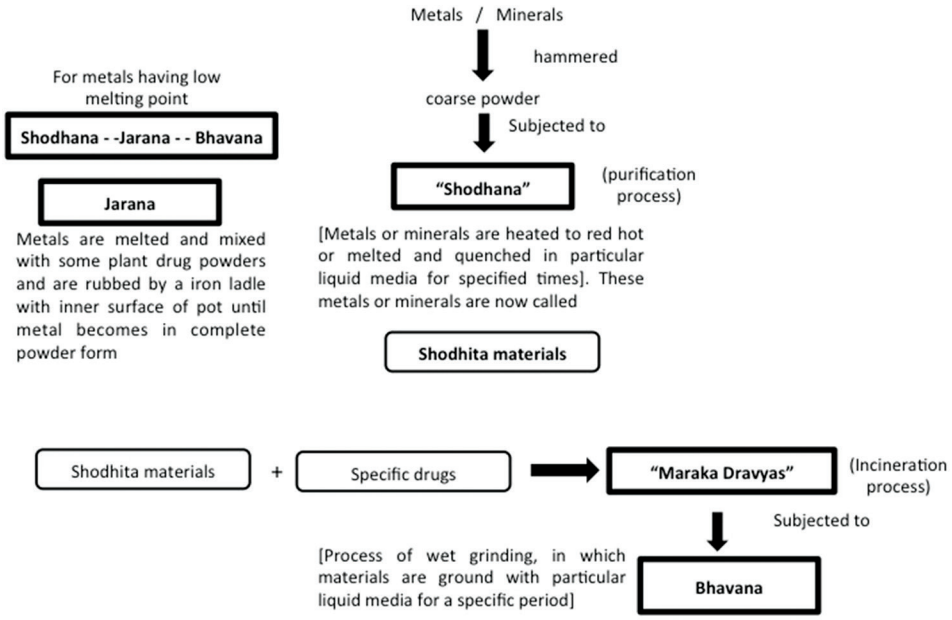

Figure 4: Processing of minerals

Discussion

Owing to the exponential growth of nanotechnology, increased and uncontrolled human exposure through various routes intentionally or inadvertently is not a remote or unlikely situation.[20] The exposure can be by way of occupation, lifestyle and random. All the engineered nanoparticles are not meant for human use the way *Bhasma* preparations were meant. The nanoparticles however are one of the miracle inventions, the safety aspect of which for human use and ecosystem at large cannot be disregarded. We share our concern over safety assessment of nanoparticles for human use with a number of agencies globally as listed earlier. These should be treated as a new chemical, and safety data should be generated by novel strategies adapted for these novel particles. The demand for NP to be considered as a new compound needs to be corroborated by laboratory data to which regulatory agencies are open. The evaluation of engineered nanoparticles in terms of Ayurvedic *Rasayana Shastra* norms for *Bhasma* in terms of various physico-chemical attributes can be useful. Our observations of few tests like *Rekhapurntva*, *Nirdhumtva*, *Varitaratva* for the engineered nanoparticles of ZnO, and TiO_2 indicated that the engineered nanoparticles yielded similar results like *Bhasma* (unpublished data). In addition to the tests regarding the fineness, other chemical criteria for a range of engineered nanoparticles, green synthesized nanoparticles, can be checked as compared to the conventional nanoparticles, that is, *Bhasma*. *In vitro* laboratory studies on cell culture can be done in order to check the comparative effects in terms of toxicity, growth kinetics, chromosomal and DNA damage based on OECD prescribed endpoints for new drug compounds. This data will help determine the effect of manufacturing methods on cellular toxicity.

The benefits of nanoparticle-based inventions are undeniable and unstoppable hence, safety related studies should also be carried out rigorously and planned in order to provide guidelines for safer manufacturing practices.

Conclusion

The reports of miracle medicinal properties of *Bhasma* in ancient literature are not difficult to accept given proper manufacturing norms are followed. The ethno medicine practices regarding *Bhasma*, the conventional nanoparticles, may be evaluated as a potential prototype when dealing with manufacturing and usage of engineered nanoparticles, the safety of which is a major concern and not yet fully addressed.

References

1. Love SA, Maurer-Jones MA, Thompson JW, Lin YS, Haynes CL. Assessing nanoparticle toxicity. Annu Rev Anal Chem (Palo Alto Calif) 2012;5:181-205.
2. Hristozov DR, Zabeo A, Foran C, Isigonis P, Critto A, Marcomini A, *et al.* A weight of evidence approach for hazard screening of engineered nanomaterials. Nanotoxicology 2014;8:72-87.
3. The Royal Society and The Royal Academy of Engineering. Possible adverse health, environmental and safety impacts. Nanoscience and Nanotechnologies: Opportunities and Uncertainties. Ch. 5. 2004. Clyvedon Press, Cardiff UK, Latimer Trend Ltd. Plymouth UK.
4. Yu JX, Li TH. Distinct biological effects of different nanoparticles commonly used in cosmetics and medicine coatings. Cell Biosci 2011;1:19.
5. GAO. Food Safety: FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe (GRAS). Washington, DC: Government Accountability Office; 2010. Available from: http://www.tinyurl.com/5r62bu7. [Last accessed on 2011 Feb 12].
6. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Carbon black, titanium dioxide, and talc. IARC Monogr Eval Carcinog Risks Hum 2010;93:1-413.
7. National Toxics Network, Submission regarding SCCS opinion on zinc oxide (Nano Form), Oct. 2010. Available from: http://www.ntn.org.au [Last accessed on 2013 June 30]
8. Sarkar PK, Chaudhary AK. Ayurvedic *Bhasma*: The most ancient application of nanomedicine. J Sci Ind Res 2010;69:901-5.
9. Kapoor RC. Some observations on the metal based preparations in the Indian system of medicine. Indian J Tradit Knowl 2010;9:562-75.
10. Chaudhary A. Ayurvedic Bhasma: Nanomedicine of ancient India – Its global contemporary perspective. J Biomed Nanotechnol 2011;7:68-9.
11. Singh V, Garg AN. Availability of essential trace elements in Ayurvedic Indian medicinal herbs using instrumental neutron activation analysis. Appl Radiat Isot 1997;48:97-101.
12. Marri RA, Naik M. Standardization of Bhasma-importance and prospects. J Pharm Res 2011;4:1931-3.
13. Paul S, Chugh A. Assessing the role of Ayurvedic 'Bhasms' as ethno medicine in the metal based nanomedicine patent regime. J Intell Property Res 2011;16:509-15.
14. Choudhary F, Iqbal Z, Khan T, Ashraf M. Trace metals analysis in selected pharmaceutical multimineral formulations. Pak J Pharm Sci 2005;18:40-3.
15. Bhattacharya B. Elucidating the nanomaterialistic basis for Ayurvedic Bhasmas using physicochemical experimentation. J Biomed Nanotechnol 2011;7:66-7.
16. Vagbhata, Rasaratnasamuchchaya, Rasendraparibhasha, 8/27-31. edited by Indradev Tripathi, 1st ed. Chaukhamba Sanskrit Bhavan, Varanasi, 1998; 127-8.
17. Valodkar M, Jadeja RN, Thounaojam MC, Devkar RV, Thakore S. Biocompatible synthesis of peptide capped copper nanoparticles and their biological effect on tumor cells. Mater Chem Phys 2011;128:83-9.
18. Valodkar M, Rathore PS, Jadeja RN, Thounaojam M, Devkar RV, Thakore S. Cytotoxicity evaluation and antimicrobial studies of starch capped water soluble copper nanoparticles. J Hazard Mater 2012;201-202:244-9.
19. Valodkara M, Nagarb PS, Jadejac RN, Thounaojamc MC, Devkarc RV, Thakore S. Euphorbiaceae latex induced green synthesis of non-cytotoxic metallic nanoparticle solutions: A rational approach to antimicrobial applications. Colloids Surf A Physicochem Eng Asp 2011;384:337-44.
20. Oberdörster G, Maynard A, Donaldson K, Castranova V, Fitzpatrick J, Ausman K, *et al.* Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy. Part Fibre Toxicol 2005;2:8.

How to cite this article: Palkhiwala S, Bakshi SR. Engineered nanoparticles: Revisiting safety concerns in light of ethno medicine. Ayu 2014;35:237-42.

Source of Support: Nil, **Conflict of Interest:** None declared.

हिन्दी सारांश

पारंपरिक उपचार के संदर्भ में अर्वाचीन नैनोकण– लाभ एवं सुरक्षा संदर्भ विश्लेषण

सुहानी पालखीवाला, सोनल आर. बक्षी

नैनोकण इस सदी का एक चमत्कारिक संशोधन है, जिसने कई क्षेत्रों में संभावनाओं के द्वार खोजे है। हालांकि नैनो कणों से मनुष्यो, पौधो, पशुओं, मिट्टी मे रहनेवाले सूक्ष्म जीवाणुओं एवं पर्यावरण पर होने वाले प्रभाव को लेकर कई प्रश्न उठाए जा रहे है। नैनोकणों के सुरक्षित उपयोग से संबंधित प्रश्नों के उत्तर ऐसे वैज्ञानिक प्रयोगों के द्वारा दिए जा सकते है, जो किसी भी संभावित दुष्परिणाम का आकलन कर कणों ऐसे प्रयोग संबंधित क्षेत्र मे नियमन के लिए उपयोगी होंगे। ऐसा भी सुझाया जा रहा है कि पारंपारिक रूप से उपयोग मे लाए जा रहे यौगिकों के नैनो स्वरूप का एक नए पदार्थ के रूप में अध्ययन होना चाहिए और उनके सुरक्षित उपयोग के लिए भी ठीक उसी तरह का नियमन–तंत्र बनाया जाना चाहिए कि जैसा रसायन नियमन के लिए है। वर्तमान समय में नैनोकणों की लोकप्रियता एवं उनके सुरक्षित उपयोग के संदर्भ में इस लेख मे प्राचीन धातुतत्व पर आधारित भस्मों पर ध्यान केन्द्रित किया गया है। वर्तमान में पर्यावरण के अनुकूल तरीके से नैनोंकणो को तैयार किए जाने को इस लेख में आयुर्वेदिक रसायन शास्त्र में बताए गए तरीके से तुलना की गई है। नैनो तकनीक के संभावित लाभों से इन्कार नही किया जा सकता पर साथ ही उनके सुरक्षित उपयोग को सुनिश्चित करना भी आवश्यक है। यह सब देखते हुए यह अनिवार्य है कि नैनो कणों की उत्पादन प्रक्रिया एवं उनके सुरक्षित उपयोग पर संशोधन उन तकनीकों से किया जाए जो विशिष्ट रुप से इन नए पदार्थों के लिए विकसित की गई हो।