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International Journal of Pharmacognosy and Chinese Medicine
ISSN: 2576-4772

The Scope of Nano-Silver in Medicine: A Systematic Review

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Review Article

Volume 2 Issue 2

Received Date: March 12, 2018

Published Date: April 03, 2018

Abstract

Nano-silver has already been clinically explored in ancient medicine i.e ayurveda in the form of Raupya bhasma/rajat bhasma. The resurgence of nano-silver has revolutionized not only as upcoming drug against anti-microbial drug resistant nosocomial infections , but has also evolved in diagnostics, targeted drug delivery, nano-implants, nano-fillers in dentistry, nano-cement in bones and as antiseptic and dis-infectants. Several clinical trials have demonstrated their promise in bio-medical field for above mentioned areas. The only limitation observed in studies is its cumulative potential resulting in toxicity of silver known as argyria i.e grey black discolouration of skin. Moreover few studies have proved the presence of small quantities of heavy metals e.g mercury, arsenic, lead etc in ayurvedic formulations. Therefore, more toxicity studies are required to establish the safety and efficacy of nano-silver. Once toxic profile of nano-silver is established, it would be easy to apply uses of nano-silver firmly in various clinical aspects in medicine.

Keywords: Nano-silver; Antimicrobial resistance; Toxicity of silver

Introduction

Nano-silver has long been recognized as a medicinal metal in ancient system of medicine i.e., ayurveda in India. In golden period of ayurveda the fine metals, minerals and their ores e.g. gold, silver, antimony, sand, gems etc were in use for medicinal purpose [1]. No exact pharmacological studies are evident so far claiming their authenticity. Very limited numbers of reverse pharmacological studies have been conducted so far to ascertain their safety and efficacy.

Traditionally, nano-silver is also known as ash of silver/Raupya bhasma/Rajat bhasma [2]. Silver has long been recognized as antibacterial drug from the time of Hippocrates. The primary ore of silver is apparently the sulphide and argentite, obtained from argentiferous galena found in the zone of secondary enrichment of earth. Silver is available as fluorides, chlorides, bromides, iodides, hydrides, oxides, sulphides, nitrites and nitrates. Once the metal has been obtained from its naturally occurring ore by reduction process, it may contain foreign elements that may alter or reduce the pharmacological properties of metal [3].

In ayurveda, Rasa-shastra is the branch of medicine dealing with processing and therapeutics of metals and minerals drugs [4]. It lays down the various processes used for the conversion of metal and minerals into organo-metallic biocompatible form which can be easily absorbed, distributed, metabolized and excreted by human body [5]. Organo-metallic preparations are processed using physical, chemical and biological methods to make them biocompatible [6]. The ashes of metals thus obtained are actually the nano sized particles known as Bhasmas in

ayurveda. Bhasmas have been reported to contain high concentration of heavy metals [7]. But ayurvedic experts claim bhasmas to be safe for human use. According to Rasashastra these nano sized bhasmas/ashes undergo various processes e.g. purification of metal/mineral followed by levigation using some herbal extracts and repeated calcinations till the loss of impurities in final formulation [8]. Since ayurveda caters to about 80% of the population in developing countries as per the estimate of World Health Organization (WHO) [2]. Therefore, now ayurvedic formulations are being evaluated for their safety and efficacy by reverse pharmacological approaches to prove their safety. Europe has banned almost all ayurvedic products due to lack of adequate studies on safety data of such products [9].

Nanosilver (NS)/ash of silver, is constituted by aggregates of silver atoms ranging in diameter from 1 to 100 nm. Nanosilver Is the broad term used for nanospheres or colloidal NPs, nanocrystals [10,11]. The fruit extract of Emblica officinalis and leaf extract of Achlypha indica, azadirachta indica, coriandrum sativum etc are used as reducing agents to synthesize nano-silver in laboratory. Latter bear excellent antimicrobial activity against E. coli and V. cholera [12-14].

Scope of Nano-Silver

Nano silver is gaining popularity owing to its antibacterial, antifungal, anti-inflammatory and analgesic properties [15]. Scope of nano-silver is expanding day by day and is emerging as a new area of research in medicine. The use of nano-silver is highly commercialized in garment industry where it is incorporated into fabrics for neutralization of odor-forming bacteria [16]. Apart from that, NS has been incorporated into food storage containers for preventing food spoilage over long term storage as preservative by inhibiting microorganism growth [17]. The potential of nano-silver in infection prophylaxis and treatment is now under consideration due to emergence of antimicrobial drug resistance [18-20].

Silver has been used for gonococcal infections in newborns since historical era. Silver sulfadiazine is the golden remedy in the topical treatment of burn patients [21,22]. Due to indiscriminate use of anti-microbial agents, leading to resistant hospital acquired infections, there has been seen a resurgence of interest in the area of nano-silver [23].

The clinical use of nano-silver is limited due to its toxicity profile as shown in many in-vitro studies. There is a need to standardize the nano-silver formulations to reduce toxic potential [24]. There is increasing interest in nano-silver based diagnostic and therapeutic implications in medical science. With nanotechnology, the particle size of silver has been reduced to the nano scale with large surface area-to-volume ratios leading to greater and easy penetration of silver across membranes of microbes. This further increases the efficacy against many bacteria and few fungi. Anti-viral activity of nano-silver is still questionable and research in this area is still in infancy [24-26] (Table 1).

Sr. no	Modern nano-silver preparations	Traditional silver preparations (Raupya/rajat bhasmas)
1.	Modern nano-silver particles are prepared by green synthesis approaches using physical, chemical & biological methods through nanotechnology [14].	*Bhasma* means an ash obtained through incineration, repeated calcinations followed by purification which involves incorporation of some other minerals and/or herbal extracts. Bhasmas are actually synthesized using physical and chemical methods [8].
2.	Particle size of silver produced ranges from 1-20nm [12]	Bhasmas are generally with particle size of 10-15nm and are prescribed with honey, ghee or some other herbal medicines [2,6,8].
3.	Green synthesis approaches include polyethylene glycol, glucose, starch as reducing agents. Biological methods using some fungi, lactobacilli and lichens which reduce silver to nanosilver. These methods are eco-friendly and do not pose toxicity to living systems and environment [14].	There is a lack of standardization of bhasmas may lead to various toxicities in living systems [7,9]. Silver bhasmas can accumulate in skin and deeper organs leading to toxicity known as argyria [2].

	 Nano-silver salt (Modern)	 Raupya bhasma (Traditional)

Table 1: Comparative aspects of modern nano-silver and traditional silver preparations (Raupya/rajat bhasmas).

The present review is focused on emerging use of nano-silver in the field of medicine especially in diagnosis and therapeutics. We would also try to incorporate toxic aspects of nano-silver.

Applied Aspect of Nano-Silver in Diagnostics and Therapeutics

Nano-silver is the upcoming drug which has a very significant role in diagnosis and treatment of disease.

Role in diagnostics and targeted drug delivery: Studies on new targeted nano-silver as contrast agents for imaging have proved their role in early detection of atherosclerotic plaque at molecular level. Thus in future it will be possible to facilitate customized medicine by collaborating imaging and targeted nano-silver delivery approach [27,28]. Nanosilver also has plasmonic properties (light scattering, absorbance and coupling), which make it suitable as Biosensors. Nanosilver biosensors can effectively biosense a large number of proteins that normal biosensors hardly detect. This unique propery of nanosilver can be used for detecting various abnormalities and diseases in the human body at molecular level, including cancers [29,30].

The advantage of nanosilver in imaging is that do not undergo photobleaching in contrast to fluorescent dyes. Nano-silver biosensors can effectively be used to monitor cellular events over an extended period of time [29].

Targeted drug delivery using nano-silver is an important area of research these days .The aims of using nano-silver in drug delivery includes:

a) Specific cell targeting and drug delivery
b) To reduce the toxicity of other concomitant drugs e.g cancer chemotherapy
c) To maintaining therapeutic effects
d) to enhance the safety and efficacy of drug
e) Provide platform for fast development of new safe medicine [31].

The plasmonic nature of nanosilver can also be used to destroy cancer cells. The cells can be conjugated to nano-silver coated anti-cancer drugs, which then absorb light and convert it to thermal energy. The resultant thermal energy can lead destruction of targeted cancer cells [32-34].

Role in prophylaxis and treatment of infections: Nano-silver particles can easily cross cell membranes and biological fluids within the human body [2]. Nano-silver in the form of ash of silver has been in use as an antimicrobial agent since time immemorial in the form of metallic silver, silver nitrate, silver sulfadiazine for the treatment of burns, wounds and several bacterial infections. All forms of silver exhibit broad spectrum antibacterial activity against both gram positive and gram negative bacteria. In ancient Greece silver was used to purify drinking water [35-37].

Moyer had introduced the use of silver nitrate (0.5%) for the treatment of burns. According to him, silver possess antibacterial activity against Pseudomonas areuginosa, and Escherichia coli and Staphylococcus aureus [21,22].

Nano-silver has a potential to act as fungicide against Aspergillus, Candida and Saccharomyces [38]. Ales Panacek, et al. [25] has demonstrated effect of nano-silver pathogenic strain of Candida species by determining the minimum inhibitory concentration and minimum fungicidal concentration. They concluded antifungal activity against Candida spp. at the concentration of 1mg/l of Ag [25].

Hippocrates, advocated the dusting of silver powder on infected wounds and ulcers to expedite healing. Silver has been used since World War I in wound dressings for faster healing and alleviation of inflammation and pain [39,40].

Humberto H Lara, et al. [41] have given some evidences regarding anti-viral activity of nano-silver [41]. Sun and colleagues showed that nano-silver has cytoprotective effect towards HIV-1-infected helper cells. Nanosilver may interfere with the fusion of the viral membrane, thus inhibits viral penetration into the host cell.

Nano-Silver Impregnated Surgical Dressing/ Meshes and Equipments

In the modern era of nanotechnology, there is a trend of using of Nano-silver impregnated dressings with the base of foam, hydrocolloid gel, gauze or film. U.S. Food and Drug Administration (FDA) have cleared many of such nano-silver impregnated dressings [42]. The nano-silver ladden dressing change colour when the antibiotic is released. This dressing has great potential in treating burn patients who are susceptible to toxic shock syndrome. With the advent of such system, there can be a reduction in antibiotic resistance. Silver nanoparticles impregnated ointment healed the wound in 3 days in contrast to any normal ointment (control), that took 7 days to heal [39,42]. Nano-silver is used in bone cements that are used as artificial joint replacements. Nano-silver coated polypropylene mesh is said to have good antimicrobial activity and can be an ideal candidate for surgical meshes [43,44]. Due to broad spectrum of antimicrobial activity of nano-silver nanoparticles, it is used in disinfectants and hand washes [45]. Nano-silver coated intravenous catheters, endotracheal tubes, bone cements, contraceptive devices, wound dressings and dental fillings are being used these days to prevent microbial infections [46-51].

Mode of anti-microbial action of Nano-silver

The proposed mechanisms of antimicrobial property till date are:

a) Uptake of free nano-silver in microbial (bacteria, fungi) machinery followed by disruption of ATP production, DNA replication and inhibiting bacterial/fungal functional proteins [52].

b) Generation of Reactive oxygen species (ROS) and free radicles, which cause direct damage to cell membranes [53].

There are certain reports regarding mode of action of nano-silver against viral infections, where nano-silver inhibits fusion of virus with host cell. The positive charge on the Ag+ ion is critical for its antimicrobial activity. Ag+ being positively charged has high affinity to bind to negatively charged microbial cell membrane. Limitation of nano-silver is that excess of nano-silver gets deposited in host cells leading to its toxicity, known as argyria [54,55]. Sondi, et al. [52] reported that concentration of nano-silver is the deciding factor for its anti-microbial potential. Once nano-silver in adequate concentration enters microbial cell wall , it results in formation of pits in the cell wall of bacteria; consequently disturbing the membrane permeability, progressive release of lipopolysaccharide molecules and membrane proteins resulting in cell death [52-55].

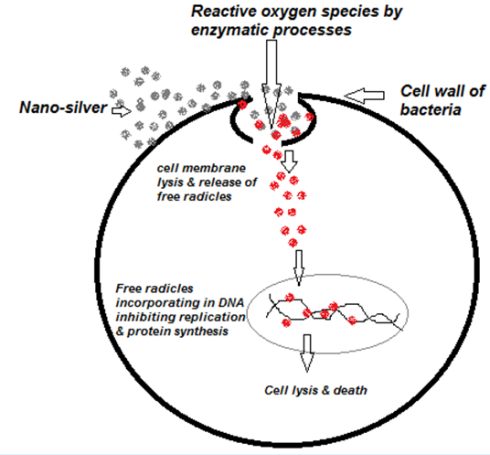

Figure 1: Diagram showing the effect of nano-silver on bacterial cell.

Role of Nano-Silver in Dentistry

In dentistry, dental nano-silver robots are gaining attention, which may be utilized for treating hypersensitive teeth, in the identification and destruction of pathogenic bacteria residing in plaque. The technology can also be helpful to design nanocomposites with nanofillers for enhanced durability of aesthetics and impressions material with nanofillers for precise tissue detail [56-58].

Discussion and Conclusion

The medical properties of silver have been known for over 2,000 years. The unique properties of nano-silver are attributed to the physical and chemical processes it undergoes during its synthesis. Nano-silver thus obtained imparts excellent antimicrobial properties. Several studies on nano-silver have demonstrated anti-bacterial, antifungal, antiviral, anti-inflammatory and analgesic properties. Owing to these beneficial effects, nano-silver has emerged as a new drug in the field of medicine for various medical applications e.g. Anti-microbial drug, targeted drug delivery in cancer chemotherapy, intravenous nano-silver coated catheters, in dentistry and many more. Still extensive research is required to fully understand their exact mechanism of action, synthesis, characterization, and possible risk of toxicity. As we know that in vitro conditions are very much different from in vivo conditions, the results obtained in in vitro studies cannot be completely applicable to living systems. Therefore, long-term toxicity studies of nano-silver must be conducted to establish the quantum of risk associated with toxicity. This would facilitate prescribers regarding the dose limit to be used in human for an indication. Thus

it can be concluded that nano-silver may be the excellent choice especially against anti-microbial drug resistance and hospital acquired infections, if used with precaution keeping in mind the toxic aspects.

Conflict of interest: The authors declare that there is no conflict of interest regarding this study.

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