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Nano Silver Particles in Biomedical and Clinical Applications : Review

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Nanotechnology is most promising arena for generating new applications in medicine and advancing rapidly due to the great progress achieved in various fileds including electronics, machanics, cosmetics, food, etc. In order to successfully bifunctionalise nanoparticles for a given biomedical application, a wide range of chemical, physical and biological factors are to be taken into account. Silver nanoparticles (AgNPs) at nanoscale exhibits strong antibacterial activity vowing to their large surface to volume ratios and crystallographic surface structure. Nanosilver particles have been widely used in a range of biomedical applications including diagnosis, treatment, medical device coating, drug delivery and personal health care products. With the growing application of nanosilver particles in medical contexts, it is becoming necessary for a better understanding the mechanisms of action, biological interactions and their potential toxicity on exposure. This review aims to provide critical assessment of the current understanding of antibacterial activity, biomedical and clinical applications of silver nanoparticles.

Key words: Antibacterial, , Biomedical, Clinical, Nanosilver, Applications.

Nanotechnology is defined as the design, characterization and application of structures, devices and systems by controlling shape and size at nanometer scale level (ranging from 1 to 100 nm) (Wong 2010; Ge et al. 2014). A nanometer is one billionth of a meter (10^{-9} m). Nano-size particles of less than 100 nm in diameter are currently attracting increasing attention for the wide range of new applications in various fields of industry. Silver nanoparticles (AgNPs or nanosilver) have attracted increasing interest due to their unique physical, chemical and biological properties compared to their macro-scaled counterparts (Sharma, Yngard, and Lin 2009b). AgNPs have distinctive physico-chemical properties, including a high electrical and thermal conductivity, surface-enhanced Raman scattering, chemical stability, catalytic activity and non linear optical behaviour (Tran 2013; Krutyakov et al. 2008). These properties are made use in production of inks, microelectronics, and medical imaging devices (Monteiro et al. 2009; Ankita Mahakalkar 2014). Also, silver nanoparticles exhibit broad spectrum bactericidal and fungicidal activity that has made them extremely popular in a diverse range of consumer products including plastics, soaps, pastes, food and textiles, increasing their market value (Singh and Nalwa 2011). Furthermore, silver nanoparticles are being used as antimicrobial agents in many public places such as railway stations and elevators in China, and they are said to show good antimicrobial action (Prabhu and

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Poulose 2012). According to the Project on Emerging Nanotechnologies PEN, over 1628 manufacturer-identified, nanotechnology-enabled products have entered the commercial market place around the world from 30 different countries. Among them, there are 383 products utilizing nanosilver (24% of products listed), this has made nanosilver the largest and fastest growing class of nanoparticles (**Fig 1**) in consumer products applications (http://www.nanotechproject.org).

In broadest definition, antibacterial is an agent that interferes with the growth and reproduction of bacteria and antibacterial activity is related to compounds that locally kill bacteria or slow down their growth without being in general toxic to target tissue (Hajipour et al. 2012). In general, agents that can slow down bacterial growth are classified as bactericidal or bacteriostatic. Antibacterial agents are paramount to fight infectious diseases. However, with their extensive use and abuse, the emergence of bacterial resistance to antibacterial drugs has become a common phenomenon, which is a major problem leading to drug resistance (Longo et al. 2013). Resistance is an evolutionary process taking place during, for example, antibiotic therapy, and leads to inheritable resistance. In addition, horizontal gene transfer by conjugation, transduction or transformation can be a possible way for resistance to build up (Witte 2004). It is a well-known fact that bacteria upon over exposure to drug develop resistance and to the fact that bacteria developed resistance against many common antibacterial agents, infectious diseases continue to be one of the greatest health challenges worldwide. In addition, drawbacks for conventional antimicrobial agents are not only the development of multiple drug resistance, but also adverse side effects. Furthermore, drug resistance enforces high-dose administration of antibiotics, often generating intolerable toxicity. This has prompted the development of alternative strategies to treat bacterial diseases. Among them, nanoscale materials have emerged as novel antimicrobial agents. Especially, several classes of antimicrobial NPs and nanosized carriers for antibiotics delivery have proven their effectiveness for treating infectious diseases, including antibiotic-resistant ones, in vitro as well as in animal models (Huh and Kwon 2011). This review in particular discusses the recent developments, current perceptive and biological actions of the silver nanoparticles. Furthermore, the application of silver nanoparticles in clinical medicine will be described.

Mechanisms of action of Silver nanoparticles

The utilization of silver as a disinfecting agent is not new, and silver compounds were shown to be effective against both aerobic and anaerobic bacteria by precipitating bacterial cellular proteins and by blocking the microbial respiratory chain system (George, Faoagali, and Muller 1997; Ian 2007). The chief structural differences lie in the organization of a key component of the membrane, peptidoglycan. Gram-negative bacteria exhibit only a thin peptidoglycan layer (<“2–3 nm) between the cytoplasmic membrane and the outer membrane ; in contrast, Gram-positive bacteria lack the outer membrane but have a peptidoglycan layer of about 30 nm thick (Shockman and Barrett 1983; Johnson, Fisher, and Mobashery 2013). Nanoparticles show good antibacterial properties arising from their large surface area to volume ratio providing desirable contact with bacterial cell membranes (Reidy et al. 2013). The mechanism of bactericidal effect of silver ions and AgNPs on micro-organisms remains to be understood. Several studies propose that AgNPs may attach to the surface of the cell membrane disturbing permeability and respiration functions of the cell (Sharma, Yngard, and Lin 2009a). The possible mechanisms of action are

1. Better contact with the microorganism-nanometer scale silver provides an extremely large surface area for contact with bacteria. The nanoparticles get attached to the cell membrane and also penetrate inside the bacteria(Bryaskova et al. 2011).
2. Bacterial membranes contain sulfur-containing proteins and AgNPs, like Ag+, can interact with them as well as with phosphorus-containing compounds like DNA, perhaps to inhibit the function (Morones et al. 2005; Matsumura et al. 2003).
3. Silver (nanoparticles or Ag+) can attack the respiratory chain in bacterial mitochondria and lead to cell death (Sondi, Goia, and Matijevi 2003).
4. AgNPs can have a sustained release of Ag+ once inside the bacterial cells (in an environment with lower pH), which may create free radicals and induce oxidative stress, thus further enhancing their bactericidal activity (Morones et al. 2005).

Such interactions in the cell membrane would prevent DNA replications, which would lead to bacterial death (**Fig 2**).

Biomedical Applications of silver nanoparticles

Nanomedicine, the application of nanotechnology to healthcare holds great promise for revolutionising medical treatments and therapies in areas such as imaging, faster diagnosis, drug delivery and tissue regeneration, as well as the development of new medical products. Indeed, materials and devices of nanometric dimensions (1–100 nm) are already approved for clinical use and numerous products are being evaluated in clinical trials (Zhang 2008). Nanosilver particles are generally smaller than 100nm and contain 20-15,000 silver atoms. At nanoscale, silver exhibits remarkably unusual physical, chemical and biological properties. Due to its strong antibacterial activity, nanosilver coatings are used on various textiles but as well as coatings on certain implants. Further, nanosilver is used for treatment of wounds and burns or as a contraceptive and marketed as a water disinfectant and room spray. Thus, use of nanosilver is becoming more and more widespread in medicine (**Fig 3**) and related applications(Chen and Schluesener 2008).

Nanosilver in diagnosis and imaging

In the last decade, the field of molecular diagnostics has witnessed an explosion of interest in the use of nanomaterials in assays for gases, metal ions, DNA and protein markers for many diseases. Intense research has been fueled by the need for practical, robust, and highly sensitive and selective detection agents that can address the deficiencies of conventional technologies.

Chemists are playing an important role in designing and fabricating new materials for application in diagnostic assays (Rosi and Mirkin 2005). Nanomaterials offer significant adavantages over conventional diagnostic systems with regard to sensitivity, selectivity and practicality. Zhou et al. (Zhou et al. 2011) developed a silver nanoparticle array biosensor for clinical detection of serum p53 in head and neck squamous cell carcinoma. This is the first clinical application of localized surface plasmon resonance (LPSR) using triangular silver nanoparticle array in head and neck squamous cell carcinoma (HNSCC). AgNPs are also employed to produce dual-imaging/therapy-immunotargeted nanoshells to locate cancer cells which can absorb light and selectively destroy targeted cancer cells through photothermal therapy (Loo et al. 2005). In addition, AgNPs can detect the interaction between amyloid ^{2}-derived diffusible ligands (ADDL) and the anti-ADDL antibody, which are related to the development of Alzheimer's disease (Haes et al. 2004).

In early cancer detection, Au–Ag nanorods were used in a recent study as a nanoplatform for multivalent binding by multiple aptamers, so as to increase both the signal and binding strengths of the aptamers in cancer cell recognition. The molecular assembly of aptamers on the nanorods was shown to lead to a 26-fold higher affinity than the original aptamer probes (Huang, Neretina, and El Sayed 2009). Thus, these nanorod–aptamer conjugates are highly promising for use in specific cell targeting, as well as having the detection and targeting ability needed for cell studies, disease diagnosis, and therapy.

Nanosilver in theraupeutics

Wound Dressing

Wound healing is regarded as a complex and multiple-step process involving integration of activities of many different tissues and cell lineages (Martin 1997). The most well documented and commonly used application of silver nanoparticles for this is in the use of wound dressings. Acticoat® is the first commercial wound dressing made up of two layers of polyamide ester membranes covered with nanocrystalline silver (Reidy et al. 2013). Silver in the form of nanoparticles seems to promote healing and achieve better cosmetic results (compared with the other silver compounds tested). The proposed mechanism is that silver nanoparticles facilitate the proliferation and migration of keratinocytes, reduce the formation of collagen by fibroblasts and modulate the number of cytokines produced (Wong 2010). Intrestingly, nanosilver is very effective fungicide as well as having antiviral properties (Galdiero et al. 2011). In the study of (Wright et al. 1999) the nanocrystalline silver-based dressing Acticoat® Antimicrobial Barrier dressing was confirmed to provide the fastest and broadest-spectrum fungicidal activity among all tested wound dressings (including those containing silver nitrate or silver sulfadiazine). It also overcomes several problems associated with previously used wound-dressings,

Table 1. Summary of select studies concerning the antimicrobial effects of AgNPs

Chemistry	Size (Average)	Zeta Potential	Organism tested	MIC	Proposed Mechanism	Reference
Silver	21 nm	N/A	*E. coli, Vibrio cholerae, Salmonella typhi, P.aeruginosa*	All reduced 100% at 75 µg/mL	Membrane disruption, Ag ion interference with DNA replication	Morones et al. 2005
Silver	Triangles (50 nm)	Positive (no value, cationic surfactant)	*E. coli*	Reduced 99% with 0.1 ¼g/mL added to agar surface	Membrane disruption, Ag ion interference with DNA replication	Zhou et al. 2011
Silver	12 nm	Negative no value	*E.coli*	Reduced 70% with 10 ¼g/mL in agar	Membrane disruption, Ag ion interference with DNA replication	Sondi et al. 2003
Silver	13.5 nm	-0.33 mV	*S. aureus, E. coli*	Inhibitory concentration of 3.56 ¼g/L and 0.356 ¼g/L, respectively, added to agar surface	Membrane disruption, Ag ion interference with DNA replication	Loo et al. 2005

like tissue irritation and insufficiently wide spectrum of antifungal properties. Sibbald et al. (Sibbald et al. 2007) conducted a prospective study to evaluate the use of silver nanoparticles dressing on a variety of chronic non-healing wounds. The study concluded that silver nanoparticles dressing has a beneficial effect of protecting the wound site from bacterial contamination. Compared with other silver compounds, AgNPs seem also to promote healing and achieve better cosmetics after healing. Taken together, the use of silver nanoparticles in the aspects of wound healing seems to hold the greatest promise.

Silver impregnated catheters

The central venous catheter (CVC) is a commonly used device in managing acutely ill patients in the hospital. They can become colonised with viable micro-organisms within 24 h of insertion, which can rapidly form biofilm. This colonisation is a precursor of catheter-related bloodstream infections (CR-BSI), which are associated with substantial morbidity, mortality, prolonged hospital stay and increased cost. Antimicrobials have been

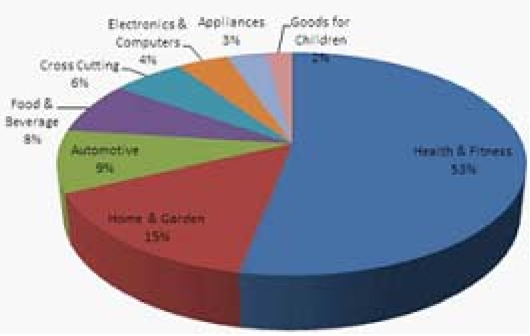

Fig.1. Nanoparticles production in different categories

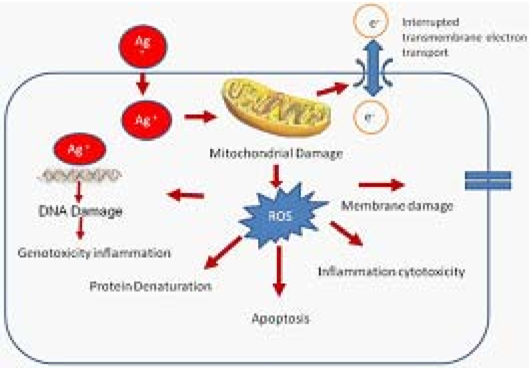

Fig.2. Illustration of toxicity mechanisms of nanparticles mediated by ROS response

incorporated into the bulk material of CVC or applied to their surfaces as a coating in an attempt to reduce the incidence of CVC colonisation and infection. Bloodstream infections are major complications in patients who require a CVC. Several infection control measures have been developed to reduce bloodstream infections, one of which is CVC impregnated with various forms of antimicrobials (either with an antiseptic or with antibiotics) (Lai et al. 2013). It was shown that the overall rate of catheter-related blood stream infections was significantly lower when silver impregnated central venous catheters (CVC) than in the conventional format (Wong 2010). Nonetheless, there is a risk that the increasing use of antibiotic-impregnated catheters could lead to eventual bacterial resistance. A new generation of silver-impregnated catheters based on the use of an inorganic silver powder, on which silver ions are bonded with an inert ceramic zeolite, has become available for clinical use. In a recent study comparing these silver-impregnated catheters with standard catheters in terms of incidence of catheter-related blood stream infections, it was shown that overall colonization rate was significantly lower in the silver-impregnated CVC tips. In addition, tip colonization by coagulase-negative *staphylococci* in the silver-impregnated CVC was lower. It would therefore appear that silver-impregnated catheters are destined for increasing use (Khare et al. 2007).

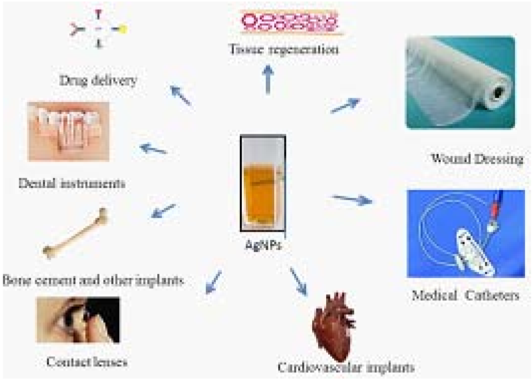

Fig.3. Biomedical applications of silver nanoparticles

Surgical Mesh

Surgical meshes are used to bridge large wounds and for tissue repairs. Though these meshes are effective, they are susceptible to microbial infections. One million nosocomial infections occur each year in patients with prosthetic devices. To decrease the prosthetic infection rate, multiple antibacterial coatings have been developed for use on medical devices such as urinary catheters, endotracheal tubes and central venous catheters. Silver nanoparticle-coated polypropylene mesh is said to have good antimicrobial activity and can be considered an ideal candidate for surgical meshes (Cohen et al. 2007). Furthermore, coating devices with an antibacterial barrier would provide another layer of protection to help decrease the iatrogenic infection rate. Darouiche (Darouiche 2004) reported that nanocrystalline silver has tremendous potential as an antibacterial coating to decrease the one million nosocomial infections a year seen in patients with implanted prosthetic materials. Moreover, (Bhol and Schechter 2005) demonstrated that topical formulation of nanocrystalline silver particles obligate anti-

Table 2. Nanoparticle characterization

Technique	Characterization Technique	Information provided
Microscopic	AFM	Size, morphology, surface texture, electrical and mechanical properties
	STM	Elemental and molecular composition
	SEM	Surface, size, shape morphology, crystallographic composition
	TEM	Elemental composition, electrical conductivity
X ray based techniques	XAS, XRF, XPS, XRD	Surface, crystallographic, and elemental composition
Light Scattering	DLS	Particle
Spectroscopic techniques	UV- visible	Size, aggregation, structure, surface chemistry

inflammatory properties in a guinea pig model of atopic dermatitis with efficacy comparable to that of high potency steroids, tacrolimus and pimecrolimus. The potential anti-inflammatory mechanism of nanocrystalline silver particles is secondary to suppression of tumor necrosis factor-± and Interleukin (IL)-12 and induction of inflammatory cell apoptosis.

Recently, Nanolabs based in United States (http://nanolabs.us/news/viewstory/55/) announced the development of innovative hemostatic mesh, which creates a mechanical barrier stopping blood flow in wounds and integrates both physical and chemical protection, and antibacterial properties. The surgical mesh material is biocompatible, durable, and flexible enough to fit complex wounds is stable and functional at extreme temperatures, has a long shelf life, and possesses antibacterial properties.

Antibacterial coatings

Infections arising from bacterial adhesion and colonization on medical device surfaces are a significant healthcare problem. Silver based antibacterial coatings have attracted a great deal of attention as a potential solution (Taheri et al. 2014). Medical device-associated infections are mainly caused by bacterial attachment and colonization of the device surface. For this reason, it is well accepted that preventing bacterial adhesion to the device surface through the application of an antibacterial coating is a potential solution (Hetrick and Schoenfisch 2006). Presently, there is substantial research in silver coated medical devices (Rai 2009). This is mainly driven by the fact that silver is active against both Gram-positive and Gram-negative bacteria and resistance has not been yet been convincingly demonstrated for clinically-relevant pathogens (Reidy et al. 2013; Ge et al. 2014). For more on the extensive efforts on development of silver based antibacterial coatings, we refer the reader to several instructive recent reviews on the topic (Samberg and Nancy 2014; Chen and Chatterjee 2013; Ravindran, Chandran, and Khan 2013).

Recently, Taheri et al., (Taheri et al. 2014) reported on the development of a silver nanoparticles based antibacterial surface that can be applied to any type of material surface. The silver nanoparticles were surface engineered with a monolayer of 2-mercaptosuccinic acid, which facilitates the immobilization of the nanoparticles to the solid surface, and also reduces the rate of oxidation of the nanoparticles, extending the lifetime of the coatings. The coatings had excellent antibacterial efficacy against three clinically significant pathogenic bacteria i.e. *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa.* Besides, studies with primary human fibroblast cells showed that the coatings had no cytotoxicity in vitro. Collectively, these coatings have an optimal combination of properties that make them attractive for deposition on medical device surfaces such as wound dressings, catheters and implants.

Furthermore, Ho et al., (Ho et al. 2013) described the application of AgNPs incorporated into amphiphilically-modified hyperbranched polylysine (HPL) as controlled releasing antimicrobial coatings for surgical poly (glycolic acid) (PGA) suture. These coatings showed a constant release of silver ions over more than 30days. After this period of washing, the sutures retained their high efficacies against bacterial adhesion. Cytotoxicity tests using L929 mouse fibroblast cells showed that the materials are basically non-cytotoxic and can be applied in preparation of antimicrobial equipment of medical for surgical suture.

Recently, antibacterial coatings on catheters for acute dialysis were obtained by an innovative and patented silver deposition technique (Pollini et al. 2011) achieved for acute haemodialysis. The surface of catheter was decorated with AgNPs by photoreduction deposition. As-obtained material was characterized by good stability and high activity against *E. coli* after 30 days of soaking in water flow.

Nanosilver as antiviral agents

Viruses represent one of the leading causes of disease and death worldwide (Galdiero et al. 2011). Although the principal mechanism underlying the viral inhibitory activity of nanosilver particles is not yet fully understood, AgNPs are considered to be a broad-spectrum agent against a variety of viral strains including HIV -1, hepatitis B virus, respiratory syncytial virus, herpes simplex virus type 1, and monkeypox virus (Ge et al. 2014). It has been observed that AgNPs have higher antiviral activity than silver ions, due to species difference as they dissolve to release Ag^0 (atomic) and Ag^+ (ionic) clusters, whereas silver salts release Ag+ only (Taylor, Ussher, and Burrell 2005). Infact (Elechiguerra et al. 2005) were the first to describe the antiviral activity of silver nanoparticles and they found that nanoparticles undergo size-dependent interactions with HIV-1. The most probable sites for interaction were found to be the sulfur-bearing residues of the gp120 glycoprotein knobs, which being limited in number, may also explain the inability of larger nanoparticles to bind the virus. Besides, silver ions can form complexes with electron donor groups containing sulfur, oxygen, or nitrogen that are normally present as thiols or phosphates on amino acids and nucleic acids and inhibit post-entry stages of infection by blocking HIV-1 proteins other than gp120, or reducing reverse transcription or proviral transcription rates by directly binding to the RNA or DNA molecules. Furthermore, Silver nanoparticles are proved to be virucidal to cell-free and cell-associated HIV-1 as judged by viral infectivity assays (Lara et al. 2011). HIV infectivity was effectively eliminated following short exposure of isolated virus to silver nanoparticles. These properties make silver nanoparticles a potential broad-spectrum agent not prone to inducing resistance that could be used preventively against a wide variety of circulating HIV-1 strains. Further in vitro and in vivo studies are warranted to elucidate the mechanisms of action which may render possible antiviral development of AgNPs as broad spectrum in treatment of infectious diseases to humans.

Other Medical applications

Silvernanoparticles find application in the diagnosis and treatment of cancer, joint replacement compounds (bone cement), dental materials, cardiovascular implants, anti inflmmatory agents, antifungal agents, contact lenses and can act as drug carriers that can deliver therapeutic agents (Liu et al. 2012; Grunkemeier, Jin, and Starr 2006; Morley et al. 2007; Yamamoto et al. 1996; Kim et al. 2008; Tien et al. 2008). The use of nanosilver in combination with vanadium oxide in battery cell components is one example of advanced silver nanotechnology improving battery performance in next-generation active implantable medical devices (Etheridge et al. 2013). Since the shape, size, and composition of AgNPs can have significant effects on their function and possible risks to human health, extensive research is needed to fully understand their synthesis, characterization, and possible toxicity.

CONCLUSION

Silver nanoparticles are inevitable as they are of substantial scientific and economic potential. The major contribuiting factors comprise shape, size and composition and can have significant effect on their function and possible risks to human health. Significant research has to be focused on this new emerging and exiciting field to address the safety issues of in vivo applications as discussed. In the next decade, it is anticipated that new materials, methods and technologies promote further development and use of silver nanoparticles in particular to serve more effective in health care system. In this review, we first gave an overview of mechanism of action of silver nanoparticles, then reviewed biomedical and clinical applications of silver nano particles.

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