

Nanosilver particles in medical applications: synthesis, performance, and toxicity

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Abstract: Nanosilver particles (NSPs), are among the most attractive nanomaterials, and have been widely used in a range of biomedical applications, including diagnosis, treatment, drug delivery, medical device coating, and for personal health care. With the increasing application of NSPs in medical contexts, it is becoming necessary for a better understanding of the mechanisms of NSPs' biological interactions and their potential toxicity. In this review, we first introduce the synthesis routes of NSPs, including physical, chemical, and biological or green synthesis. Then the unique physiochemical properties of NSPs, such as antibacterial, antifungal, antiviral, and anti-inflammatory activity, are discussed in detail. Further, some recent applications of NSPs in prevention, diagnosis, and treatment in medical fields are described. Finally, potential toxicology considerations of NSPs, both in vitro and in vivo, are also addressed.

Keywords: nanosilver particles, synthesis, biomedical application, toxicity

Introduction

Nanosilver particles (NSPs) generally present at 1 to 100 nm in size in at least one dimension.¹⁻⁴ As particle size decreases, the surface area-to-volume ratio of NSPs increases dramatically, which leads to significant changes in their physical, chemical, and biological properties. NSPs have been among the most commonly used nanomaterials in our health care system for hundreds of years. Recently, NSPs have become of intense interest in biomedical applications (Figure 1), because of their antibacterial, antifungal, antiviral, and anti-inflammatory activity.^{5,6}

NSPs have been widely used for diagnosis,⁷ treatment,⁸ drug delivery,⁹ medical device coating,¹⁰ wound dressings,¹¹ medical textiles,¹² and contraceptive devices.¹³ As the use of nanosilver products is continually increasing, a better understanding of nanosilver biological interactions and their toxicity becomes necessary. This review critically discusses NSP synthesis methods, properties, and current and emerging medical NSP applications. Finally, recent advances concerning NSP potential toxicity will also be described.

NSP synthesis

Different synthetic NSP routes lead to variable sizes, shapes, morphology, and even stability. Generally, these methods can be classified into three broad categories: physical, chemical, and biological (or green) synthesis.

Physical synthesis

Evaporation/condensation and laser ablation are the main physical techniques for deriving nanosilver from metal samples. The evaporation/condensation technique uses a furnace

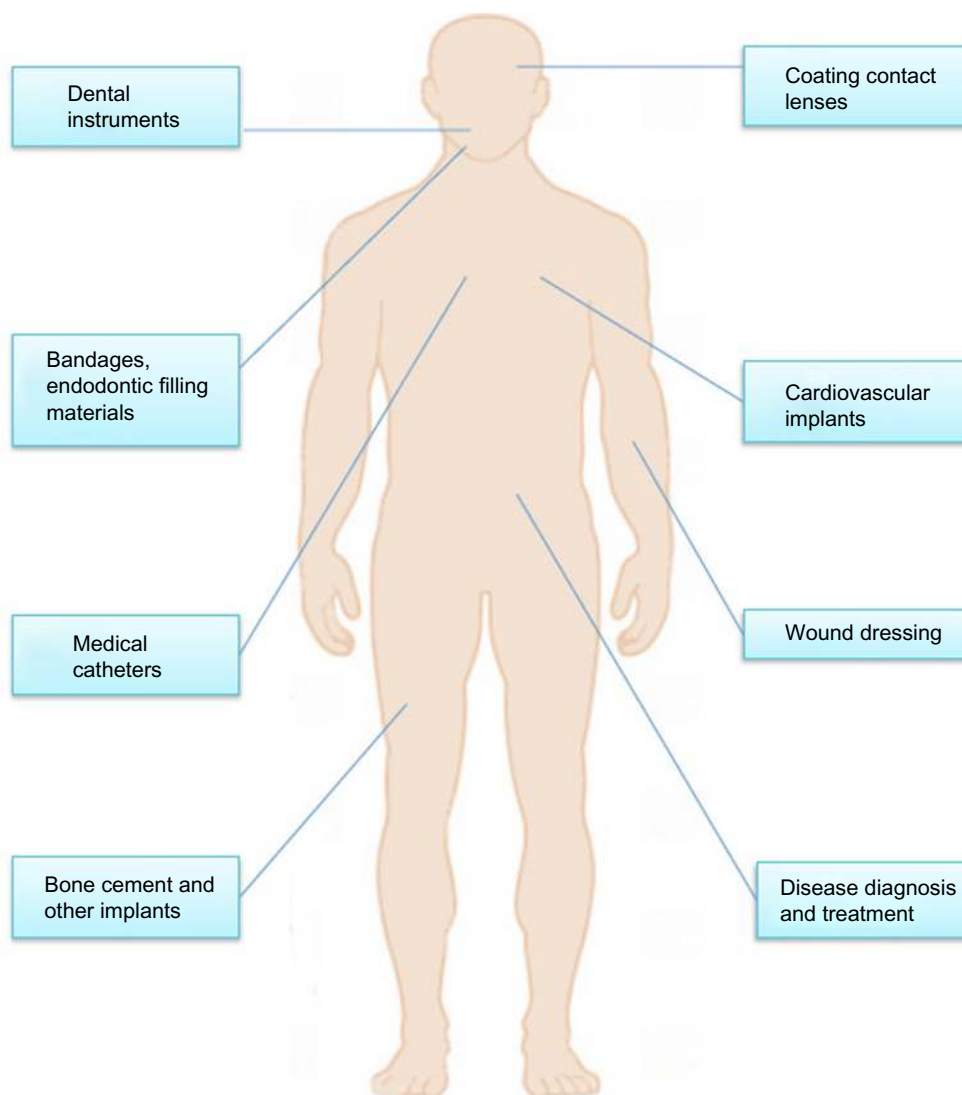


Figure 1 Biomedical applications of nanosilver particles in human health care.

tube under atmospheric pressure to produce NSPs; however, conventional furnace tubes have several drawbacks, such as high energy consumption, and require a long time to achieve thermal stability. Jung et al used a small ceramic heater with a local heating area, thus the evaporated vapor could cool at a suitable rate and a high concentration of nanosilver could be obtained.¹⁴ Laser synthesis employs the laser ablation of metals in solution without chemical reagents, which leads to pure nanosilver colloids.¹⁵ The concentration and morphology of nanosilver are affected by laser fluence and the number of laser shots. Greater laser fluence and amount of time, lead to larger particle size and higher particle concentration.¹⁶ Recently, Tien et al reported a novel arc-discharge method of producing silver suspension in pure water without any surfactants or stabilizers.¹⁷ In their research, silver wires were utilized as positive and negative electrodes and etched in pure water.

During discharge, the surface layer of the silver wires was evaporated and condensed in the water, thus stable and well-dispersed NSPs of 20–30 nm in size were obtained.¹⁷

Chemical synthesis

Chemical reduction is the most frequent method of nanosilver synthesis, and uses silver salt, reductants, and a stabilizer or capping agents as three main components to control NSP growth (Figure 2). Among these, silver nitrate is a silver salt that is often used for NSPs, due to its low cost and chemical stability compared to the other available silver salts.¹⁷ The reductants include borohydride,¹⁸ citrate,¹⁹ ascorbate,²⁰ and hydrogen gas.¹¹

Borohydride is a strong reducing agent that can result in small particles with a faster reduction rate, because borohydride can also act as an NSP stabilizer and avoid aggregation

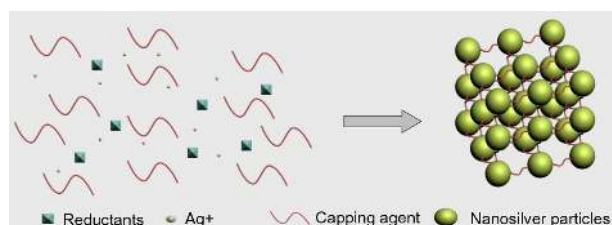


Figure 2 Chemical synthesis of nanosilver particles.

Abbreviation: Ag, silver.

of NSPs during its decomposition.¹¹ It is hard to obtain high concentrations of NSPs because of their aggregative instability. Using a stabilizer in preparation is a common strategy. The stabilizers include surfactants and ligands or polymers that contain functional groups such as polyvinylpyrrolidone, poly(ethylene glycol), poly(methacrylic acid), poly(methyl methacrylate), and others. Furthermore, temperature-sensitive polymers such as poly(N-isopropylacrylamide) and collagen can also serve as stabilizers, and nanosilver capped by those chemicals allows for novel thermal switching applications.¹

NSPs can also be synthesized in a two-phase water-organic system. This method produces uniform and controllable nanoparticles. In this system, metal precursor and reducing agent are separated in two phases, thus the rate of interaction can be controlled by the intensity of interphase transport between aqueous and oil phases; however, large amounts of surfactant and organic solvent may contaminate the surface of formed NSPs, and the removal of surfactant and organic solvent is also time-consuming and expensive.

Biological synthesis

Biosynthesis (green synthesis) of nanosilver has received extensive attention due to the growing need for environmentally

friendly synthesis methods that use eco-friendly reducing and capping agents, such as protein;²¹ peptides;²² carbohydrate;²³ various species of bacteria,²⁴ fungi,²⁵ and yeast;²⁶ and algae and plants.²⁷ For example, Naik et al synthesized NSPs of 60–150 nm in size using silver-binding peptides identified from a combinatorial phage-display peptide library. The peptides were placed in an aqueous solution of 0.1 mM silver nitrate for 24–48 hours at room temperature.²¹ Thomas et al developed an economical, fascicled, and in situ approach to prepare large-scale chitosan–nanosilver (400 nm) films using chitosan as a chelating and stabilizing agent; the films demonstrated excellent antibacterial action against *Escherichia coli* and *Bacillus*.²⁸ Sintubin et al reviewed different biological synthesis methods using microorganisms or plants for nanosilver synthesis.²⁶

In biological synthesis, as the reducing agents and stabilizers are molecules produced by protein, carbohydrate, bacteria, fungi, yeasts, algae, or plants, organic solvents and toxic reagents are avoided. The possible mechanism of biological synthesis includes enzymatic and non-enzymatic reduction (Figure 3). Nicotinamide adenine dinucleotide phosphate-dependent reductase can produce NSPs by enzymatic reduction; however, the enzymatic reduction rate is often slow (between 24 and 120 hours).²⁹ The non-enzymatic reduction of silver is similar to chemical reduction, but the reducing and stabilizing agents are microorganisms or plants. Non-enzymatic reduction is usually fast, often completed within a few minutes, and can handle extreme parameters, such as high pH or high temperature, that accelerate the synthesis.²⁴

The main advantage of biogenic synthesis over other methods is that the green synthesis avoids organic solvents and toxic reagents. Thus, biosynthesized NSPs are more stable than

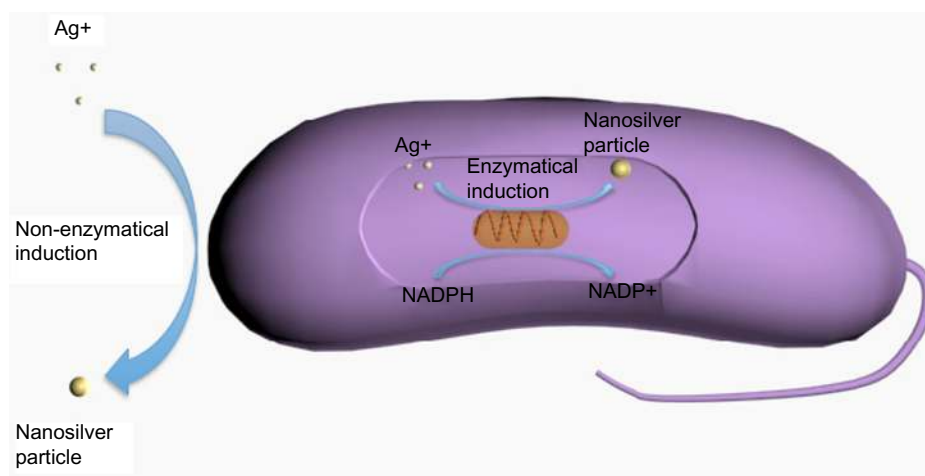


Figure 3 Biological (or green) synthesis of nanosilver particles.

Abbreviations: NADP⁺, nicotinamide adenine dinucleotide phosphate (oxidized form); NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); Ag, silver.

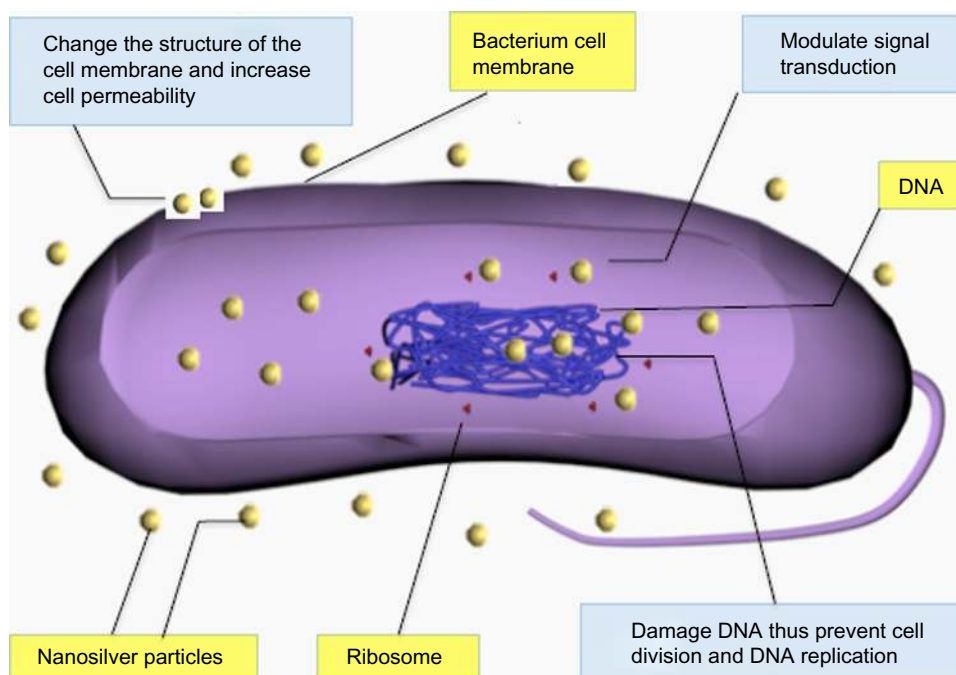


Figure 4 Antibacterial mechanism of nanosilver particles.
Abbreviation: DNA, deoxyribonucleic acid.

those that are chemically produced, and they can remain stable over a long period of time.³⁰ In addition, biological synthesis makes it possible to produce NSPs under a nontoxic silver nitrate concentration because microbial cells can continue to multiply;³¹ however, the biosynthesis drawback is that the purification process may lead to pathogenic bacteria and the potential bacteria may cause contamination, which should be a reason for exercising caution in medical application.²⁶

NSP performance

Antibacterial properties

NSPs have a broad antibacterial effect on a range of Gram-negative and Gram-positive bacteria and antibiotic-resistant bacteria strains.³² Antimicrobial efficacy of NSPs depends on their size and concentration. Normally, a high concentration leads to more effective antimicrobial activity, while particles of small sizes can kill bacteria at a lower concentration. Apart from size and concentration, shape also influences the antimicrobial efficiency of NSPs. Sadeghi et al investigated the antimicrobial activity of different nanosilver shapes, which included silver nanoplates, silver nanorods, and silver nanoparticles, on *Staphylococcus aureus* and *E. coli*. They found that silver nanoplates had the best antimicrobial activity.³³ It has also been reported that NSPs combined with various antibiotics have better antimicrobial effects than NSPs or antibiotics alone. Li et al, for example, found a greater antibacterial effect on

E. coli when amoxicillin and silver nanoparticles were combined than when they were applied separately.³⁴

Although the antimicrobial effect of nanosilver has been widely studied, the exact mechanism of NSPs is still elusive. It is widely accepted that NSPs can anchor to and subsequently penetrate the bacterial cell wall, thereby causing structural change of the cell membrane and increasing cell permeability, leading to cell death (Figure 4).³⁵ The formation of free radicals and subsequent free radical-induced membrane damage is another potential mechanism, which has been investigated by Kim et al.³² It has also been found that NSPs can release silver ions and interact with the thiol groups of many vital enzymes and phosphorus-containing bases, thus inhibiting some functions in cells, such as preventing cell division and DNA replication.³⁶ In addition, NSPs may modulate signal transduction through changing the phosphotyrosine profile of bacterial peptides for the potential antibacterial mechanism (Figure 4).³⁷

Antifungal properties

Nanosilver is an effective antifungal agent against a broad spectrum of common fungi. Kim et al investigated NSP antifungal properties on a total of 44 strains of six fungal species, and found that NSPs can inhibit the growth of *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, and *Trichophyton mentagrophytes* effectively.³⁸ Nasrollahi et al³⁹ and Kim et al⁴⁰ observed that

NSPs can disrupt cellular membrane and inhibit the normal budding process; however, the exact mechanisms of action of nanosilver against fungi are still not clear.

Antiviral properties

NSPs are also an antiviral agent against HIV-1,⁴¹ hepatitis B virus,⁴² respiratory syncytial virus,⁴³ herpes simplex virus type 1,⁴⁴ and monkeypox virus.⁴⁵ It has been observed that NSPs have higher antiviral activity than silver ions, due to species difference as they dissolve to release Ag⁰ (atomic) and Ag⁺ (ionic) clusters, whereas silver salts release Ag⁺ only.⁴⁶ Lara found that the anti-HIV mechanism of nanosilver is based on the inhibition of the initial stages of the HIV-1 cycle.⁴⁷ NSPs can bind to glycoprotein (gp)120, thus inhibit cluster of differentiation (CD) 4-dependent binding, fusion, and infectivity. They act as an effective virucidal agent to block HIV-1 cell-free and cell-associated infection. Furthermore, NSPs inhibit post-entry stages of the HIV-1 life cycle.⁴⁷ Although the mechanism underlying their viral-inhibitory activity is not yet fully understood, NSPs could be considered to be a broad-spectrum agent against a variety of viral strains and are not prone to developing resistance.

Anti-inflammatory properties

NSPs show anti-inflammatory properties in both animal models and in clinic. For example, in the swine model with contact dermatitis induced by topically applying 1,2-dinitrochlorobenzene, nanosilvers altered the expression of proinflammatory cytokines transforming growth factor- β and tumor necrosis factor- α .⁴⁸ Shin and Ye found that NSPs attenuated nasal symptoms in allergic rhinitis mice and inhibited OVA-specific immunoglobulin E, IL-4, and interleukin-10, and that inflammatory cell infiltration and goblet cell hyperplasia were inhibited by nanosilvers.⁴⁹ In a human clinical study, wound dressing containing NSPs promoted the healing of chronic leg ulcers by not only reducing bacteria numbers in the wound bed, but by decreasing inflammatory response as well.⁸ NSPs' ability to reduce cytokine release and matrix metalloproteinases,^{8,50} decrease lymphocyte and mast cell infiltration,⁴⁸ and induce apoptosis in inflammatory cells^{8,49} may explain their anti-inflammatory mechanisms.

Medical NSP applications

Wound dressings

Robert Burrell developed the world's first commercially available nanosilver product (Acticoat™; Smith and Nephew, London, UK) to treat various wounds in clinic, including burns, chronic ulcers, toxic epidermal necrolysis,

and pemphigus.⁵¹ Huang et al observed that NSP-loaded wound dressings significantly reduced the healing time by an average of 3.35 days and increased bacterial clearance from infected wounds compared to silver sulfadiazine, with no adverse effects;⁵² however, Chen et al showed that nanosilver-loaded wound dressings could enhance healing in superficial burn wounds but made no difference in deep burn wounds, compared with 1% silver sulfadiazine.⁵³ This suggests that NSPs accelerate reepithelialization but not angiogenesis.

Currently, new dressings are being fabricated with the aim of increasing antibacterial efficacy and promotion of wound healing. For example, Lu et al developed a wound dressing composed of NSPs and chitosan, and found that it significantly increased wound healing during treatment of deep partial-thickness wounds and inhibited infection, as well as diminished the risk of silver absorption, compared with 1% silver sulfadiazine dressings.⁵⁴

Cardiovascular implants

The first cardiovascular medical device containing silver in clinic was a prosthetic silicone heart valve coated with silver element, which was designed to prevent bacterial infection on the silicone valve and to reduce inflammation response;⁵⁵ however, metal silver may cause hypersensitivity, inhibits normal fibroblast function, and leads to paravalvular leakage in patients.⁵⁶ NSPs are safe and nontoxic in medical devices, unlike metal silver. Therefore, Andara et al synthesized a new nanocomposite with NSPs and diamond-like carbon as a surface coating for heart valves and stents, and found that the surface of the nanocomposite showed antithrombogenic and antibacterial properties.⁵⁷ In addition, Ghanbari et al⁵⁸ and Fu et al⁵⁹ also constructed antibacterial multilayer films containing NSPs, and investigated their antibacterial, mechanical, and hemodynamic properties in vitro for use in cardiovascular implant coating.

Catheters

Much research has been conducted to investigate NSPs as antibacterial materials for coating catheters, including central venous catheters and neurosurgical catheters. Silverline (Spiegelberg GmbH and Co. KG, Hamburg, Germany) and ON-Q Silver Soaker™ (I-Flow Corporation, CA, USA) are two commercially available medical catheters containing NSPs to prevent catheter-associated infections.⁵¹ Medical catheters are prone to bacterial infection, which can rapidly spread to the wound and its surrounding, and lead to serious

complications. Because of their superior antibacterial properties and lack of observed toxicity, NSPs can decrease the incidence of bacterial infection and complications after surgery, thus they have been widely accepted for use in medical catheters. Andara et al found that plastic catheter tubes coated with nanosilver could inhibit bacterium growth in vitro for at least 72 hours, with no significant toxicity, in an animal model.⁵⁷ In a pilot clinical study, 19 patients who received a nanosilver catheter did not show catheter-associated ventriculitis, and all cerebrospinal fluid cultures were negative, while five patients were positive for catheter-associated ventriculitis in the control group (20 patients).⁶⁰

Bone cement

Alt et al evaluated antibacterial activity of plain poly(methyl methacrylate) bone cement loaded with different NSP concentrations in vitro, and found that bone cement-loaded 1% nanosilver completely inhibited the proliferation of *Staphylococcus epidermidis*, methicillin-resistant *S. epidermidis*, and methicillin-resistant *S. aureus*, with no significant difference between the nanosilver bone cement and the nontoxic control group in quantitative and qualitative cytotoxicity tests.⁶¹ NSPs were also added to ultra-high-molecular-weight polyethylene for fabricating inserts for total joint replacement components, and it was found that NSPs drastically reduced the wear and tear of the polymer.⁶²

Dental materials

NSPs also have applications in dental instruments and bandages. Yoshida et al showed that a resin composite incorporated with NSP-containing materials had a long-term inhibitory effect against *Streptococcus mutans*.⁶³ Yamamoto et al also showed that a resin composite containing silver ion-implanted fillers released silver ions with antibacterial effects on oral streptococci.⁶⁴ In addition, Magalhães et al showed that incorporating NSPs in endodontic filling materials provided a significantly enhanced anti-bactericidal effect against *Streptococcus milleri*, *S. aureus*, and *Enterococcus faecalis*.⁶⁵ NSPs in dental adhesives are also very effective against streptococci without affecting the adhesive mechanical properties, thus enabling their use in orthodontic treatments.⁶⁶

Biodiagnosis

NSPs can be used for bio-diagnosis, where plasmonic properties of NSPs strongly depend on size, shape, and dielectric medium that surrounds it.⁶⁷ Zhou et al developed a silver nanoparticle array biosensor for clinical detection

of serum p53 in head and neck squamous cell carcinoma.⁶⁸ NSPs are also employed to produce dual-imaging/therapy-immunotargeted nanoshells to locate cancer cells and can absorb light and selectively destroy targeted cancer cells through photothermal therapy.⁶⁹ In addition, NSPs can detect the interaction between amyloid β -derived diffusible ligands (ADDL) and the anti-ADDL antibody, which are related to the development of Alzheimer's disease;⁷⁰ however, silver is easily oxidized and forms plasmonically unattractive compounds such as halides in biological solutions, which deteriorates the plasmonic performance of NSPs.¹⁸

Other medical applications

NSPs have applications in the diagnosis and treatment of cancer,⁷¹ and are drug carriers that can deliver therapeutic agents,⁷² which are used in eye care for coating contact lenses.¹⁷ In addition, 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.⁷³

NSP toxicity

NSPs may have potential toxicities at some concentrations and can cause various health problems if used improperly. Thus, it is necessary to address the biosafety of NSPs in human health.

In vitro toxicity

NSPs have been reported to be cytotoxic to several types of cells, including human peripheral blood mononuclear cells,⁷⁴ human alveolar epithelial cell line (A549)⁷⁵, murine and human alveolar macrophage cell line,⁷⁶ neuroendocrine cells,⁷⁷ rat liver cell line,⁷⁸ and mouse germline cells.⁷⁹ Alt et al, however, found that bone cement containing 1.0% nanosilver did not lead to significant cytotoxicity in mouse fibroblasts (L929) and human osteoblast cell line.⁶¹ Although the details of the toxic mechanism are unclear, it suggests that NSPs are ionized in the cells, which leads to activate ion channels and changes the permeability of the cell membrane to both potassium and sodium,⁸⁰ interaction with mitochondria,⁸¹ and induction of the apoptosis pathway via the production of reactive oxygen species,⁸² which leads to cell death.

In vivo toxicity

Chen and Schluesener have reviewed biodistribution, organ accumulation, degradation, possible adverse effects, and toxicity associated with the medical use of nanosilver.¹³

Respiratory tract, gastrointestinal tract, skin, and female genital tract are the main entry portals of nanosilver into the human body through direct substance exchange with the environment. Additionally, systemic administration is also a potential route of entry, since colloidal silver nanoparticles have been exploited for diagnostic imaging or therapeutic purposes. Inhalation and instillation experiments in rats showed that low concentration, but detectable, ultrafine silver (14.6 ± 1.0 nm) appeared in the lung and was subsequently distributed to the blood and other organs, such as heart, liver, kidney, and even brain.⁸³ In a recent oral toxicity study of rats, Kim et al also found that silver nanoparticles accumulated in blood, liver, lungs, kidneys, stomach, testes, and brain, but NSPs showed no significant genotoxicity after oral administration of silver nanoparticles of 60 nm average size for 28 days at different doses.⁸⁴ Lee et al showed that NSPs less than 12 nm in size affected early development of fish embryos, caused chromosomal aberrations and DNA damage, and induced proliferation arrest in cell lines of zebrafish;⁸⁵ however, Lansdown found that silver was not a cause of neurotoxic damage, even though silver deposits have been identified in the region of cutaneous nerves,⁸⁶ and Ji et al found that NSPs did not affect respiratory system in a 28-day in vivo study.⁸⁷

Animal and human studies indicate that it is difficult to remove silver completely once it has been deposited in the body; however, nanosilver can be excreted through the hair, urine, and feces.⁸⁸ There is no consensus on nanosilver's toxicity to humans, and most toxicity investigations of silver nanoparticles are based on in vitro cellular experiments and relatively short-term animal experiments.

Conclusion

NSPs represent a prominent nanoproduct and are already widely used in medical applications, including wound dressing, diagnosis, and pharmacological treatment. Since the shape, size, and composition of NSPs 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. In this review, we first gave an overview of NSP synthesis, then reviewed applications of NSPs in the field of biomedicine. Finally, possible toxicology was discussed.

There is a limited number of well-controlled studies on the potential toxicities of nanosilver, though these studies tend to suggest that NSPs can induce toxicity in living beings. It should be noted that in vitro conditions are drastically different from in vivo conditions; however, longer-term studies

and assessment of NSP toxicity must be conducted so that NSP exposure does not exceed toxic levels.

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Disclosure

The authors report no conflicts of interest in this work.

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