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Silver nanoparticles in biomedical contexts: Current insights and future directions

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Abstract
Modern applications for silver nanoparticles (AgNPs) range from nanopharmaceutics to renewable energy. Silver nanoparticles are the most well-recognized substance that may be found in all nanotechnology products. However, the accompanying toxicity to biosystems limits their application. Therefore, for AgNPs to be used effectively, their surfaces must be conjugated with biologically beneficial moieties that increase the bio-acceptability of silver-based nanosystems and other capabilities for extending their special applications. However, the biomolecule-conjugated AgNPs offer practical remedies for time-consuming clinical issues of the modern era, such as multidrug resistance, designing pharmaceuticals with improved bioavailability, superior drug delivery vehicles, and in situ bioimaging of significant metabolites that make use of the biomolecule-anchored surface-engineered AgNPs. Antimicrobial silver nanoparticles have developed as very effective agents against infection due to their ultra-small regulated size, wide surface area, and better reactivity with an active functional structure. The surface ligand coating of the silver nanoparticle used as a drug delivery vehicle highlights the medication's continuous release with little adverse effects when administered into the body. The antimicrobial effectiveness of AgNPs is influenced by several vital physicochemical factors, encompassing their dimensions, morphology, electrostatic properties, concentration, and colloidal stability. These attributes collectively shape nanoparticles' potential to combat microorganisms through diverse mechanisms. The modes of antimicrobial action encompass their attachment to microbial cells, internalization within these cells, initiation of reactive oxygen species (ROS) and free radical production, and modulation of signal transduction pathways in microbes. In the context of the present nanopharmaceutical paradigm, this review epigrammatically examines several intriguing therapeutic uses of surface-conjugated AgNPs with biomolecules such as peptides, nucleic acids, amino acids, and antibodies.

Keywords: Silver nanoparticles, nanopharmaceuticals, biosynthesis, drug resistance, antimicrobial activity

Introduction

Metallic nanoparticles consisting of noble metals, such as silver and gold, have received a lot of interest and investigation in recent years due to their distinct chemical, biological, and physical properties. The biomedical assessment of silver nanoparticles (AgNPs), which first sparked global interest as potential antibacterial agents, gained special attention. AgNPs have long been employed as antibacterial agents in the health sector, cosmetics, food storage, textile coatings, and some environmental applications, despite a lack of understanding of their toxicity and *in vivo* biological activity. AgNPs have a size range of 1 nm to 100 nm and are a type of zero-dimensional material having morphological properties. Metallic silver ions have powerful antibacterial properties, but can be easily separated through phosphate and chloride functions, proteins, and other biological components. AgNPs' inherent biocide or biostatic activity is heavily regulated by physicochemical properties such as shape, size, oxidation and dissolution states, surface charge, and coating (Burdușel *et al*., 2018; Nedelcu *et al*., 2014) [2, 9].

To investigate the efficacy of nano silver-based biomaterials as antibacterial agents, experiments were conducted on a wide range of bacteria, viruses, fungi, and yeasts, as well as other medically significant planktonic and sessile pathogenic microorganisms. AgNPs' remarkable antibacterial activity is an excellent starting point for developing innovative, high-performance nano silver-based biomedical goods such as anticancer drugs, drug delivery systems, orthopedic materials and devices, bandages, antiseptic sprays, and catheters. A detailed knowledge of AgNP's physicochemical properties, *in vitro* and *in vivo* impacts, biodistribution, safety control mechanism, and pharmacokinetics is also required for the translation of silver-based nanotechnology to clinical applications (Burdușel *et al.*, 2018; Fortunati, Peltzer, Armentano, Jiménez, & Kenny, 2013) [2, 3].

Synthesis of silver nano particles: Nanomaterials can be created using two methods: "top-down" and "bottom-up" procedures. The top-down technique starts with the material in its bulk form and reduces it to the nanoscale by specialized ablations such as lithography, thermal breakdown, laser ablation, mechanical milling, etching, and sputtering. The "bottom-up" approach to nanoparticle preparation involves a homogeneous system where catalysts, such as reducing agents and enzymes, synthesize nanostructures controlled by catalyst properties, reaction media, and conditions (e.g., solvents, stabilizers, and temperature).

1. **Polysaccharide method:** Metal nanoparticles can be manufactured via the polysaccharide approach, which involves the use of water and polysaccharides as a reducing or stabilizing agent. Silver nanoparticles can be fabricated utilizing starch as a protecting agent and β-d-glucose as a reductant in a mild heating system. At higher temperatures, the attraction between starch and silver nanoparticles weakens and is reversible, making it easier to separate the produced silver nanoparticles (Mochochoko, Oluwafemi, Jumbam, & Songca, 2013) [8].
2. **Biological method:** Biological extracts from bacteria and plants can be used to reduce or shield metal nanoparticles throughout the manufacturing process. Extracts contain a variety of biomolecules with reducing potential, including amino acids, vitamins, proteins, enzymes, and polysaccharides. These compounds are both ecologically friendly and chemically complicated. Using the unicellular green algae Chlorella vulgaris extract, single-crystalline silver nano-plates were synthesized at room temperature. The extract's proteins may serve two functions: reducing Ag+ and controlling shape during synthesis (Annamalai & Nallamuthu, 2016) [1].
3. **Bacterium-Initiated Synthesis:** Lactobacillus fermentum prevents Pseudomonas aeruginosa from forming biogenic silver nanoparticles and limits biofilm growth. B. flexus nanoparticles produced both spherical (12 nm) and triangular (61 nm) anisotropic nanoparticles. To utilize AgNP with B. cereus, incubate for 3-5 days at ambient temperature. AgNP generation and durability were dependent on psychrophilic bacteria's cell-free culture supernatants. Bacillus thuringiensis spore crystal fusion produces AgNPs with a 15 nm (cube and hexagonal) mixed form. Using *Escherichia coli*, *Klebsiella pneumonia*, and Placonema boryanium UTEX 485 with aqueous AgNO3 resulted in the precipitation of spherical silver nanoparticles after 28 days, depending on temperature, pH, and concentration factors. The interaction between silver ions and bacteria affects the size and shape of silver nanoparticles created utilizing microorganisms (Iravani, 2014) [6].

Effect of silver nano particles as antimicrobial agents

AgNPs' intrinsic physical and chemical properties, such as maintaining dispersion and stability and inhibiting aggregation, are important parts of their specific antibacterial activity. Numerous studies have demonstrated that silver nanoparticles (AgNPs) have superior anti-pathogenic activity to silver ions. Pathogenic drug resistance is an alarming and developing phenomenon that raises serious concerns about the global healthcare system. AgNPs are thus an excellent contender for the development of unique, highly effective, biocompatible nanostructured materials for novel antibacterial applications based on nanotechnology. AgNPs are one of the most widely used metallic nanoparticles in modern antimicrobial applications due to their innate strong bactericidal activity against both gram-negative and gram-positive bacteria, as well as their physicochemical properties (Pal, Tak, & Song, 2007) [10].

The most significant physicochemical parameters influencing AgNPs' antibacterial activity include size, shape, concentration, and surface charge. As previously stated, AgNPs demonstrate their inherent enhanced antibacterial activity through a variety of mechanisms. The fundamental advantage of nanosilver-based biomaterials created for unconventional antibacterial applications is their inherent anti-pathogenic properties exhibited against both planktonic and biofilm-organized microbes. Silver cations, which can attach to thiol groups in bacterial proteins, are assumed to be responsible for AgNPs' bactericidal activity. By doing so, they can damage the bacteria's physiological activity and trigger cell death (Li *et al.*, 2008) [7].

Effect of nanoparticles in wound healing

Wound infections are a major therapeutic problem due to their enormous impact on patient morbidity and mortality, as well as their significant financial implications. The tough and critical task of modern clinical treatment is to prevent wound dehiscence and surgical site infection. Although the skin is the largest and most complex organ in the human body, it is vulnerable to harm from a variety of external sources. Depending on the severity of the injury, physically or chemically produced cutaneous wounds can severely compromise the structural and functional integrity of the skin at various stages, resulting in permanent disability or even death. In a nutshell, new research reveals the following information about AgNP skin absorption: A wealth of experimental data supports nanoparticals' *in vitro* skin permeability, and penetration is greatly increased, which is the cause of wounded skin. Chitosan and collagen are two naturally occurring biopolymers that, when combined with novel nanotechnology processes, have enormous promise for the development of unique and functionally superior platforms for wound healing applications. Because diabetic wounds can be accompanied by a variety of secondary infections, the use of AgNPs and Ag+ carriers is also a promising method for delayed diabetic wound healing processes. Diabetes patients who utilize AgNPs benefit from reduced scarring and faster wound healing (Burdușel *et al.*, 2018; Hendi, 2011) [2, 5].

Dental and bone application

Dental caries, one of the most common oral disease-related disorders in the world, is extremely costly. Nanotechnology-based dental solutions attempt to lessen or even eliminate the clinical impact of caries by speeding remineralization and regulating biofilm formation. Materials for dental barrier membranes (DBM), which are often used for effective alveolar bone healing, must perform particular specific functions in addition to their inherent highly biocompatible behaviour. The efficiency of many metal-coated implants against the microorganisms that cause dental-related biofilm formation and eventual implant failure has been investigated. Antibacterial resins could assist both orthodontics and restorative dentistry. In orthodontics, they could be employed as filler or denture base materials, and in restorative dentistry as bracket or branked bonding materials (Burduşel *et al*., 2018) [2].

To improve the physicomechanical properties and antibacterial effects of acrylic resin denture-base materials, a technology for adding AgNPs to them was developed. The majority of human bone, dentin, and tooth enamel is composed of crystalline hydroxyapatite (HA), a calcium-phosphate salt. Given that biosynthesized and synthetic HA is highly biocompatible, this material and its derivatives are being extensively studied for the development of novel osseous-related restorative and regenerative strategies, such as synthetic bone grafts or coating materials for metallic implants. Biocompatible HA combined with silver is an appropriate alternative for the development of bioactive and antibacterial bone implants in terms of the implant's superficial surface. Gram-negative bacterial strains were tested against HA-based nanosilver coatings to determine their antibacterial efficacy. AgNPs are commonly used as doping elements in synthetic and bio-inspired bone scaffolds during bone-replacement procedures, and new research suggests that this strategy is promising (Gunputh, Le, Handy, & Tredwin, 2018) [4].

Several experimental methods, including laser-assisted deposition, electrochemical deposition, sol-gel technology, and microarc oxidation, demonstrated acceptable for the inclusion of nanosilver into calcium-phosphate materials to induce antibacterial characteristics.

Conclusion

Silver nanoparticles (AgNPs) are being actively researched as nanostructures for innovative and enhanced biomedical applications due to their size-related desirable physicochemical properties and biological usefulness, particularly their remarkable antibacterial activity and non-toxicity. AgNP-based nanosystems and nanomaterials are used for medication administration, wound dressing, tissue scaffolding, and protective coating. A large body of study evidence supports the beneficial effects of AgNPs in novel biocompatible and nanostructured materials and apparatus designed for modern treatment methods.

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