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Silver Nanoparticles for Enhancement of Antibiotic Antimicrobial Therapy

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Abstract

With the current rise in antimicrobial resistance and infections resulting in high mortality and morbidity. There is need for novel strategies to combat these challenges such as nanoparticle technology has offered excellent opportunities. The use of metal nanoparticles such as silver with well-established antimicrobial activity conjugated with other antimicrobials has the potential to overcome the challenge of drug resistance due to its multiple mechanisms of action against microbes. This reveal highlights the characteristics of silver, the antibacterial action of silver nanoparticles (AgNPs), the role of nanotechnology in improving antimicrobial activity of silver and studies conducted in relation to the use of silver nanoparticles for purposes of improving antimicrobial therapy.

Keywords: Silver nanoparticles, antibacterial activity, antibiotic therapy, antimicrobial activity, microbes, nanotechnology

INTRODUCTION

Historically all forms of silver metal have been used as antimicrobial agents either by itself or in combination with other agents [1]. Its ability to inhibit bacterial growth has rendered it useful in various aspects including pharmaceutical formulation of semi solid dosage forms incorporated as silver nitrate or silver sulfadiazine creams and dressings for treatment of burns and ulcers. Silver is also used in food industry during packaging to prevent contamination, [2–5]. Silver nanoparticles (AgNPs) are nanomaterials whose dimensions range in 1–100 nm. At nanoscale silver possess unique characteristics unlike its bulk form including higher surface. The exceptional antibacterial activity exhibited by AgNPs towards several infectious, pathogenic microorganisms including multidrug-resistant bacteria has received much attention from the scientific (medical and healthcare areas) and industrial fields [6, 7]. An enhanced antibacterial activity of silver when incorporated at a nanoscale has been observed and proved to be valuable in medical and healthcare products including surgical dressings, dental products, cosmetics, catheters [8–11].

Antibacterial Mechanism of Silver Nanoparticles

AgNPs have proved their broad-spectrum efficiency against pathogenic microbes [12]. The current experimental evidence suggests that the mechanisms of action are related to the physicochemical properties of size and surface area which enables them to interact with bacterial cell walls, membranes and directly affect intracellular components.

There are currently three mechanisms of antibacterial action evidently supported by scientific research exerted by AgNPs working either independently or together [10, 13, 14]. The first one is related to the AgNPs ability to penetrate the outer cell wall membrane. AgNPs have proved

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to interact with proteins containing sulfur on bacteria cell wall possibly causing structural damage and rupture resulting in an accumulation on the inner membrane followed by adhesion of the nanoparticles causing destabilization and damage and subsequently increased cell membrane permeability and leakage of intracellular components [15, 16]. The second mechanism proposes that AgNPs enter the cell due to its affinity for phosphorus groups in intracellular DNA and proteins this alters their structure and functions. Similarly, AgNPs have shown to interact with enzymatic thiol groups inducing reactive oxygen species and free radicals which may alter respiratory chain and activate apoptosis pathway. The third mechanism is related to the physicochemical traits of silver at the nanoscale. The mechanism suggests that the release (bioavailability) of silver ions is more pronounced due to the size and charge allowing them to effectively interact with cellular components altering their metabolic pathways, and even genetic material [17–19]. Figure 1 below gives a summative illustration of different modes of action as highlighted above.

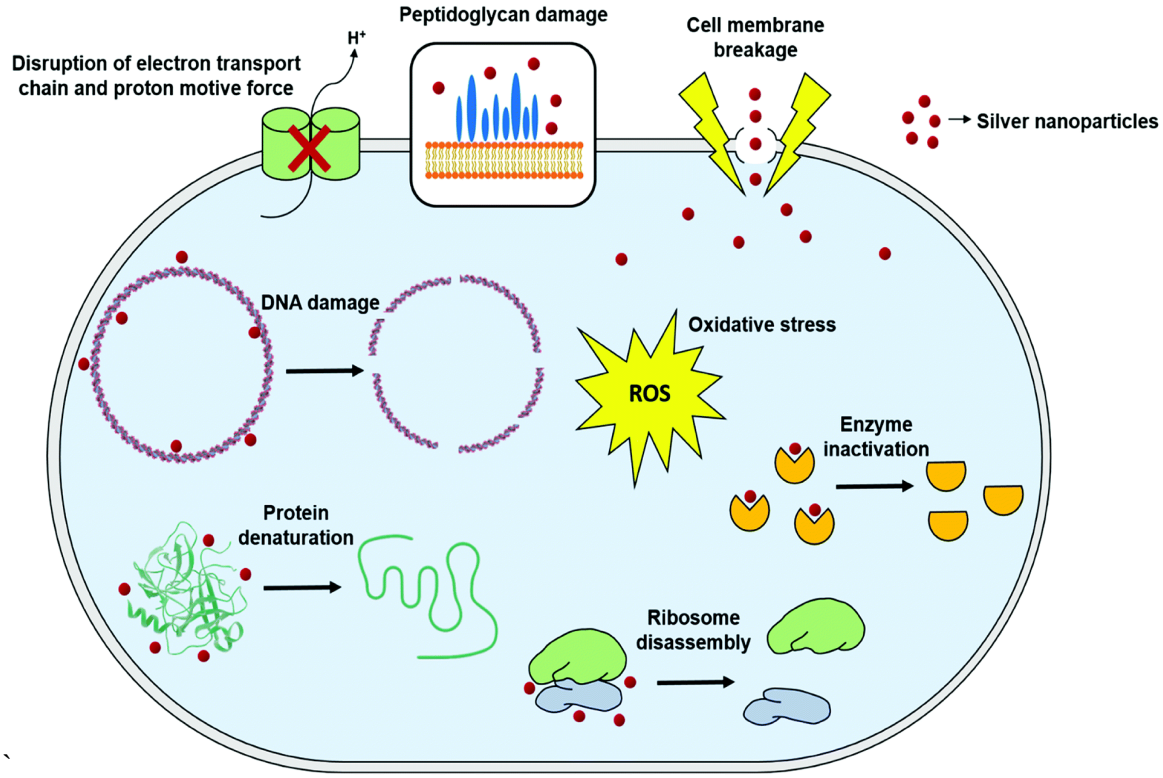

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Figure 1. Summative model of mechanism of action of silver nanoparticles AgNPs-antibiotic treatment.

CHARACTERISTICS OF SILVER

The processes associated with development of new antibiotics with an effort to combat the rise in new infections, multi- drug resistant microorganisms and mortality globally are time consuming and require a lot of resources to establish efficacy and safety of agents [16]. Hence the establishment of antibacterial mechanisms of AgNPs offers a promising alternative in the management of various disease-causing microorganisms. In relation with the fact that AgNPs have shown high grade activity against multidrug-resistant strains, AgNPs also have unique characteristics rendering them useful against these bacteria [20, 21]. Silver has shown has to be the most effective metallic nanoparticle against bacteria and other microorganisms, additionally silver has excellent biocompatibility properties hence its use in various medical products [17, 18]. The multiple mechanisms of antibacterial action associated with silver nanoparticles including cell membrane destabilization and permeation, effect on intracellular components and respiratory chain. Lastly AgNPs pose a low risk associated with development of resistance as microorganisms would have to target multiple mechanisms of action occuring in parallel. The above characteristics are at the core of AgNPs use in

antimicrobial therapy either independently or by synergistic and additive effect with other antibiotics [22, 23].

Several strategies by which bacteria have acquired to render antibiotics with no effect have been established including acquisition of resistance genes from different bacteria, biofilm formation, challenges with antibiotic permeation, the mutation of the antibiotic target sites, presence of efflux pump systems that remove the antibiotic from intracellular media and many others [24]. Interestingly, the above mechanisms do not inhibit AgNPs action, as earlier established AgNPs act by various simultaneous mechanisms including quick diffusion of minute AgNPs and Ag ions into the cell wall, cell membranes disruption and mechanical damage and modification of DNA and proteins intracellularly [16, 20, 21].

A scheme of these mechanisms is illustrated in Figure 1, this suggests that silver nanoparticles can exert their effect regardless of bacteria having resistance mechanisms. Most importantly the ability of AgNPs to inhibit formation of biofilms makes them excellent candidates for use in combination with other antibacterial compounds as they can enhance bacterial susceptibility to other antibiotics through membrane disruption, prevention of biofilm formation, and inhibition of membrane components like efflux pumps [18, 25].

Below are various studies conducted in relation to the use of silver nanoparticles for enhancing antimicrobial therapy

Vazquez-Munoz et al studied the synergistic effect of AgNPs – antibiotics hybrid systems in both Gram-positive and negative strains. The minimal inhibitory concentration of AgNPs was 10–12 μg mL^{-1} in all tested bacterial strains regardless of their different susceptibilities to antibiotics. A significant synergistic antimicrobial and additive properties were evident with the fractional inhibitory concentration index, FICI: <0.5) and (0.5 to 1) for kanamycin and chloramphenicol AgNPs complexes respectively. However, the combination of AgNPs and β-lactam antibiotics showed no effect [26]. TEM studies showed alteration of bacterial membrane and structural damage, this could explain the improvement in cell membrane permeability. Suggesting that the conjugational synergism depends on the antibiotic target site, facilitated by AgNPs. membrane structural alterations. This study offers in-depth understanding of the synergistic mechanism of AgNPs and antibiotics, aimed at combating antimicrobial infections efficiently, especially multi-drug resistant microorganisms [27].

In another study, the biocompatible non-cytotoxic concentration of AgNPs was determined to be ≤ 1 μg/mL gingival fibroblasts. The antibacterial efficacy of silver nanoparticles individually and in conjugation with 11 antibiotics was recorded against Gram positive and Gram-negative species. AgNPs at non cytotoxic concentrations ≤ 1 μg/mL showed no antibacterial activity. On the contrary, at the same concentration when conjugated with antibiotics significant bacterial growth retardation was observed even for bacteria that initially had shown resistance to either the antibiotics or AgNPs individually. These results indicate that biocompatible concentrations AgNPs can increase the antibacterial effectiveness of antibiotics against multiple bacterial species via synergism effect. Furthermore, antibiotic resistance shown by some bacterial species could be overcome by combining with AgNPs, hence broadening the overall antibacterial potential [28].

A study by Khatoon and colleagues formulated silver-ampicillin (a second-generation β lactam antibiotic) nanoparticles (Amp-AgNps) using single step synthesis. This was to combine the dual antibacterial properties of ampicillin and silver. The Amp-AgNps characterization results revealed that metallic silver is reduced into nano scale by the amine group of ampicllin Computational molecular dynamics simulation was further used to validate these results. The MIC for Amp-AgNps against 6 different bacterial strains at (3–28 μg/ml). This was much lower than that of ampicillin (12–720 μg/ml) and silver nanoparticles (280–640 μg/ml). The efficacy of Amp-AgNps following repeated exposure to bacterial strains was studied this was considering the tendency to develop resistance in bacteria against drugs with repeated exposure. The tested strains showed no resistance to Amp-AgNps

following 15 successive cycles of exposure. Further biocompatibility tests of Amp-AgNps were carried out against cell lines using Keratinocytes cell lines (HaCaT). These results disagree with a study by Vazquez-Munoz et al who reported that the combination of AgNPs and β-lactam antibiotics showed no effect. This could mean that the susceptibility could be tailored to individual β-lactam antibiotics [29].

Murei et al formulated and analysed antibacterial conjugates of AgNPs with ampicillin, penicillin, and vancomycin coupled with extracts of *Pyrenacantha grandiflora* tubers against *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella Pneumoniae*. FTIR revealed the formation of new functional groups. The conjugate of ampicillin and silver nanoparticles against *K. pneumonia* and *E. coli* showed improvement. The activity of Vancomycin conjugated with silver nanoparticles showed improvement against *K. pneumonia.* The conjugation of *this conjugate* improved the biological activities of the drugs. This further emphasizes the potential of silver nanoparticle conjugates in enhancing the biological activities of existing antibiotics [30].

Ahmad et al prepared gemifloxacin conjugated silver nanoparticles (Gemi-AgNPs) and studied their antibacterial efficiency against pathogenic bacteria. Gemi-AgNPs showed round oval shape with a particle size (22.23 ± 2 nm). The Gemi-AgNPs had excellent antimicrobial and biofilm inhibition properties against *Proteus mirabilis* (*P. mirabilis*) and methicillin-resistant *Staphylococcus aureus* (*MRSA*). Gemi-AgNPs at IC_{50} value of 57.4 ± 0.72 µg/Ml showed significant inhibition of urease. Bacterial cell morphology analysis using TEM revealed that bacterial cell membranes were disrupted and completely destroyed following treatment with Gemi-AgNPs [31].

Similarly, biocompatible AgNPs – gentamycin conjugates were prepared and tested against drug-resistant bacterial biofilm-associated infections (Gram-positive, Gram-negative, and drug-resistant bacteria). Morphological analysis showed spherical hybrid nanoparticles with a diameter of 2–6 nm. The conjugate showed significant efficiency to inhibit and disrupt bacterial biofilm. This shows that silver nanoparticle antibiotic hybrid has the future potential role in controlling drug-resistant bacterial infections [32].

Further the ability to inhibit biofilm formation and bacterial colonization of urinary Catheters using green Silver Nanoparticle was studied by Nag et al. AgNPs size range was 15–25 nm. AgNPs coated urinary catheters showed significantly inhibited bacterial growth lastig for 72 h against resistant Gram-positive (*Staphylococcus aureus and Staphylococcus epidermidis*) and Gram-negative (*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and *Pseudomonas aeruginosa*). However greater activity was associated with Gram-negative bacteria. Hence in clinical therapy treating urinary catheters with AgNPs can potentially overcome infections of the urinary tract [32].

Silver nanoparticle's ability to be synthesized using biotechnology techniques which are eco-friendly using prokaryotic microorganisms to reduce the inorganic metals has opened up exciting opportunities towards development of green nanotechnology.

Gandhi et al prepared biogenic silver nanoparticles using *Escherichia coli*. Silver nanoparticles were then combined with antibiotics and tested against microbes. Increased antibacterial activities was observed for Bacitracin against *Escherichia coli* and *Salmonella paratyphi B.* Ampicillin against *Corynebacterium diphtheriae*, Kanamycin against *Klebsiella pneumonia*, gentamycin against *Pseudomonas aeruginosa* and for Bacitracin, Gentamycin, Erythromycin, Ciprofloxacin against *Staphylococcus aureus* [33].

A study to evaluate the mechanism for the synergistic activity of conjugated silver nanoparticles (AgNPs) and an antibiotic to inhibit bacterial growth especially against the drug-resistant bacteria Salmonella typhimurium was conducted. β-lactam (ampicillin and penicillin), quinolone (enoxacin), aminoglycoside (kanamycin and neomycin), and (tetracycline) were used. Synergistic growth

inhibition against Salmonella typhimurium was observed for AgNPs conjugates of enoxacin, kanamycin, neomycin, and tetracycline on the contrary ampicillin and penicillin showed non. UV–vis spectroscopy revealed formation of complexes for all four synergistic antibiotics with AgNPs, while ampicillin and penicillin did not. Tetracycline enhanced the binding of silver metal (Ag) to Salmonella by 21% and the release of silver ions (Ag+) release by 26% compared to that without tetracycline, conversely the presence of penicillin neither enhanced the binding of Ag or Ag+ release. These findings reveal that the mechanism of interaction between antibiotics and AgNPs is complexation. These complexes then interact more strongly with the bacterial cells causing release of more Ag+, this creates a temporal high concentration of Ag+ on bacteria cell walls resulting in growth inhibition [34].

Another study Kaur et al studied the mechanism of interaction and efficacy between silver nanoparticles (AgNPs) and different antibiotics conjugates. Amikacin and vancomycin were used to conjugate AgNPs. FTIR analysis showed the presence of intermolecular hydrogen bonding between PVP-coated AgNPs and the antibiotics. Synergetic bactericidal properties were observed against Escherichia coli and Staphylococcus aureus by agar well diffusion technique [35].

Using root, stem, and leaves extracts of *Persicaria hydropiper* Ali et al prepared and analysed phytogenic- silver nanoparticles (AgNPs) activity against multidrug resistant (MDR) bacteria. A dark brownish color visulally confirmed the presence of silver nanoparticles in addition to UV–Vis and Fourier Transformed Infrared Spectroscopy (FTIR). Scanning Electron Microscopy (SEM) displayed tetrahedron to spherical and oval shapes of AgNPs and average size range of 32–77 nm. Further it was observed that the potency of antibiotics against MDR bacteria increased after coating them with AgNPs. Ceftazidime and Ciprofloxacin activity increased up to 450% and 500% against *Bacillus* respectively while Gentamicin, Vancomycin and Linezolid increased up to 150%, 200% and 58% against *Bacillus*, *Staphylococcus*, and *Proteus* species respectively [36].

Li X developed pH-responsive nanocomposites of ultrasmall silver nanoparticles (AgNPs) and kanamycin, and then coated with polydopamine (PDA@Kana-AgNPs) with an effort to overcome the challenges associated with bacterial biofilms such as causing chronic infections because antibacterial drugs have poor penetration through this dense matrix barrier causing limited entry intracellularly. Confocal fluorescence imaging revealed that PDA@Kana-AgNPs could respond to the acidic microenvironment of biofilms, resulting into biofilm-triggered on demand drug release in situ. The Resazurin assay and zone of inhibition test showed that the conjugate of kanamycin and AgNPs had greater antimicrobial activity against (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* BL21) than when applied individually. The crystal violet staining test further demonstrated that biofilms were effectively dispersed by the synthesized nanocomposites. Biocompatibility evaluation showed that PDA@Kana-AgNPs were non-toxic to mammalian cells. This study shows that the proposed pH-responsive nanocomposites hold excellent potential for efficient delivery of antibiotics and exhibited synergistic antibacterial and antibiofilm activities [37].

Vazquez-Muñoz et al further analysed the ultrastructural analysis of candida albicans on exposure to silver nanoparticles (AgNPs). A high accumulation of silver nanoparticles on the outer cell lining and smaller quantities were observed in the cytoplasm by Energy dispersive spectroscopy (EDS) analysis confirmed the intracellular silver [38].

Facile and eco-friend biogenic silver nanoparticles (b-AgNPs) and amphotericin B-conjugated biogenic silver nanoparticles (Amp-bAgNPs) were synthesized and assessed for antifungal activity. High-resolution transmission electron microscopy (HRTEM) showed well dispersed spherical silver nanoparticles and Amp-bAgNPs with an average particle size of 10 and 15 nm. Low to moderate antifungal activity (4–8 mm ± 0.2) was observed for Biogenic silver nanoparticles on the contrary amphotericin B conjugated silver nanoparticles exhibited excellent activity against *Candida albicans* (16 mm ± 1.4) and *Candida tropicalis* (18 mm ± 1.5) [39].

DISCUSSION

The potential use of silver nanoparticles for enhancement of antibiotic antimicrobial therapy is evident from the scientific literature above with nanotechnology playing a pivotal role in enhancement mechanism of both silver and antimicrobial agents against microorganisms through conjugation techniques.

Excellent synergistic and antimicrobial additive effect are evident following conjugation of AgNPs with and various antimicrobials against Gram-positive and Gram-negative bacteria [6–10]. An increase in the efficacy against pathogenic organisms of individual antimicrobials was also reported when prepared with silver nanoparticles which can be explained by the ability of silver nanoparticles to form complexes with antimicrobials which interact more strongly with the bacterial cells causing release of more silver ions (Ag+) this creates high concentrations of Ag+ on cell walls [28–34] causing further resulting into bacterial cell membranes disruption and destruction (ultrastructural damage) and consequent increase in cell membrane permeability and internalization of drugs [33–35]. Its to this effect that the reported enhanced activity of antimicrobials against resistant bacteria can be explained. Being more pronounced with antimicrobials acting inside bacteria due to increased internalization [7, 9, 24]. Hence the use of AgNPs in combination with commercially available antibiotics could provide potential alternate therapy in combating infectious diseases caused by MDR bacteria [36].

Repeated exposure of AgNps antibiotic conjugates to bacteria has not demonstrated any resistance, considering the tendency to develop resistance in bacteria after repeated exposure to antimicrobials [16–19]. This effect could be related to the mechanisms of action of these compounds [25, 26]. Unlike AgNPs antibiotics targets specific sites on bacteria. The ability of AgNPs to act at multiple cell structures or sites suggest that in the combined use of AgNPs and antibiotic, AgNPs are responsible for the initial interaction, destabilization and accumulate in bacterial cell walls and subsequently cell membranes enabling high flux of antibiotics, bacterial debilitation and possible prevention of existing resistance mechanisms since AgNPs can modify and destroy cellular barriers and protein membranes enhancing antimicrobial action by allowing antibiotics to exert their actions at both membrane and intracellular levels in addition to the synergistic or additive effects for some antibiotics [27–29], This shows the potential of silver nanoparticles in overcoming antimicrobial resistance and enhancing therapy.

Some studies have reported varying outcomes concerning the conjugation of β-lactam antibiotics with silver nanoparticles having no effect [27] and others reported enhanced susceptibility of bacteria to β-lactam lactams [28, 30], This variation can be mean that the susceptibility could be tailored to individual β-lactam antibiotics [29] and types test bacteria strain used.

Studies have further demonstrated that silver nanocomposites have also exhibited excellent activity against fungi species when conjugated with antifungal drugs. AgNPs do not penetrate the cell wall of candida species but instead releases silver ions which then infiltrate the cell leading to the formation of nanoparticles via reduction by organic compounds found on the cell wall and cytoplasm [38]. The enhanced antifungal activity of the AgNPs -antifungal hybrid system be explained by the synergistic mechanism between antifungals and antimicrobial property of silver [39]. Additionally, the ability of silver nanoparticles to inhibit biofilm formation in urinary catheters can potentially be useful in preventing urinary tract infections [32].

CONCLUSION

This encapsulation and conjugation strategy of silver nanoparticles could be used to formulate variety of antibiotics, antifungals, antivirals, and other materials to improve their potential against biofilm-related infections. The biocompatible conjugated nanoparticles of silver hold excellent opportunity as efficient drug delivery vehicles for a wide range of agents in improving the susceptibility of already resistant pathogens to antimicrobials, overcoming drug resistance, and

consequently enhancing antibiotic antimicrobial therapy**.** The need for animal infection models to evaluate the therapeutic efficiency of AgNPs-antimicrobial conjugate in combating emerging microbial infections is inevitable.

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