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Review Paper

SILVER NANOPARTICLES EFFECTIVE AS ANTIMICROBIAL AGENTS

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Abstract

Silver nanoparticles (AgNPs) are one of the most imperative and engrossing nanomaterials that are involved in biomedical applications. In nanoscience and nanotechnology AgNPs play an important role, particularly in the field of nanomedicine. Due to their peculiar physical and chemical properties (their large surface area, to volume ratio and novel antiviral and antibacterial properties), now a days silver nanoparticles (AgNPs) are the most hopeful nanoantibiotics. The precedence or favorable action of AgNPs are a generalized mode of action against different pathogens, such as viruses, bacteria and fungi. The silver nanoparticles show the antibacterial effectiveness regardless the microbial susceptibility to conventional antibiotics, including efflux pumps and biofilm formation. The aim of this article is provide the complete view of the antimicrobial properties,the action mechanism of silver nanoparticles, effects of silver nanoparticles against the various microbes.

Key words: nanomaterials, nanoparticles, nanomedicine, nanoantibiotics, efflux pump, biofilm, microbes.

INTRODUCTION

In ancient time silver was used as antimicrobial agent. Recently AgNPs in nanoscience and nanotechnology radically changed the way to diagnose, treat, and prevent various diseases in all aspects of human life. Although several noble metals have been used for various purposes, AgNPs have been focused on potential applications in cancer diagnosis and therapy[1]. A broad spectrum of activity silver has shown effectiveness of silver against more than 650 pathogens in medicine field. Its use in the form of nanoparticles intensify this property, allowing its use in a wide range of applications.[2.3,4].Nanoparticles are group of atoms, with sizes having between 1 and 100 nm, whereas a “nano” is used to indicate one billionth of a meter.[5-7].Because of

their smaller size, AgNPs have different physical and chemical properties to that of metallic silver.[2,8,9]. Due to their extra ordinary physical and chemical properties Silver nanoparticles are increasingly used in various fields, including medical, food, health care, consumer, and industrial purposes.[10,11] These include optical, electrical, and thermal, high electrical conductivity, and biological properties it is also used in medical device coatings, optical sensors, and cosmetics, in the pharmaceutical industry, the food industry, in diagnostics, orthopedics, drug delivery, as anticancer agents, and enhanced tumour-killing effects of anticancer drugs.[1,12].

Recently, green synthesis of silver nanoparticles is developing into a new and important branch of nanotechnology, it is plant-mediated. Green synthesis gained more importance now a days because it is eco environmental and effective cost, with lesser toxicity when related to chemical hazards[13,14]. Green synthesis is defined as the use of environmentally conflict materials such as bacteria, fungi and plants in the synthesis of nanoparticle. Compared with the use of plant extracts, biosynthesis of AgNPs using microorganisms requires a precise process of cultivating and maintaining microbial cells, which in some cases can be pathogenic to humans. The ease of handling, the availability and a broad viability of metabolites are among the advantages of using plant extracts. Due to the broad availability of plant extracts as well as a wide range of biodegradable biologically active metabolites, biosynthesis of nanoparticles from plant extracts is receiving great interest.[15]

History:

Since ancient times it is known that silver has antibacterial properties. The antimicrobial activity of silver appears to have been known since early in recorded history. For centuries, the antibacterial properties of silver have been used to fumigate potable water by storage in silver containers[16,17].There is anecdotal evidence for the use of Nano silver in ancient Egypt and Rome[16,18]. The Macedonians used silver plates to improve wound healing and Hippocrates used silver in the treatment of ulcers. In 1520, Paracelsus used silver internally and also applied silver nitrate as a caustic for the treatment of wounds, a practice that continues today[16,19]. In 1614, Angelo Sala administered silver nitrate internally as a counterirritant, as a purgative and for the treatment of brain infections[19] .C. S. F. Crede is credited with the first scientific publication to describe the medical use of silver in the late nineteenth century. Crede

used eye drops containing 1% silver nitrate solution to treat eye infections in new-born[18]. In the United States, colloidal Nano silver, i.e. suspensions of silver particles in liquid, which was registered in 1954 as a biocidal material has been used in medications for nearly one hundred years.[16,18,20] It has long been known that silver nanoparticles are useful in wound management, and they have been employed since the 18th century to treat ulcers. This nanomaterial with its important antimicrobial activity was regulated for wound management in the 1920s by the U.S. Food and Drug Administration[21].In his review, Neal (2008) noted several applications for silver, including wound dressings. Antimicrobial products containing silver nanoparticles are commercially available. Topical application of silver nanoparticles to wounds is responsible to promote and accelerate healing process; in 41 addition it acts as antibacterial agent playing a role in the modulation of cytokines involved in tissue repair.[21,22].

In recently generally biogenic synthesis of silver nanoparticles becomes necessary via green chemistry concepts to produce silver nanoparticles with enhanced stability[23]. Green formation of metal nanoparticles by naturally biodegradable components including polysaccharides, biopolymers, vitamins, plant extracts and microorganisms represent sustainable resources in biosynthesis of metal nanoparticles. Subsequently, using microorganisms as bacteria, fungi, microalgae and cyanobacteria in addition to plant extracts and macro algae could induce the required reduction for metal nano synthesis providing an eco-friendly, low priced technology as well as simplicity in scaling up for high production[23,24]

Synthesis of siver nanoparticles

1. In physical methods, nanoparticles are prepared by the evaporation-condensation process at atmospheric pressure using a tube heater[38,39].The two conventional physical methods are used for the synthesis of AgNPs, these methods including pyrolysis and spark discharging[40,41].The main advantages of these methods are speed and radiation which are used as reducing agents and they have less chemical hazardous, but these methods produce low yield and have high energy consumption, and solvent contamination.

2. Chemical methods use water or organic solvents to prepare the silver nanoparticles [42,43]. Generally the chemical syntheses of AgNPs are used two approaches "Top to bottom" and "Bottom to top".**1."The** Top to bottom" method involves the bulk materials which are broken down the smaller fine particles by grinding and thermal ablation while **2**."The Bottom to top "method involves the sono decomposition of metals, reduction of metals and electro chemical methods. The bottom to top approach used various chemicals to synthesized the AgNPs.[25,44,45].The chemical methods take on three essential components such as reducing agents, and metal precursors.

Biosynthesis of silver nanoparticles is a part of bottom to top approach which involves the redox reactions. The biological synthesis of silver nanoparticles involves the three major components, the solvent (green solvents), reducing agent and non-toxic materials. In biological synthesis, the AgNPs are synthesized from biological entities like microorganisms, and plant extracts. The molecules which are used in the synthesis of nanoparticles are ecofriendly and pollution free. Biological methods seem to provide controlled particle size and shape, which is an important factor for various biomedical applications.[1]

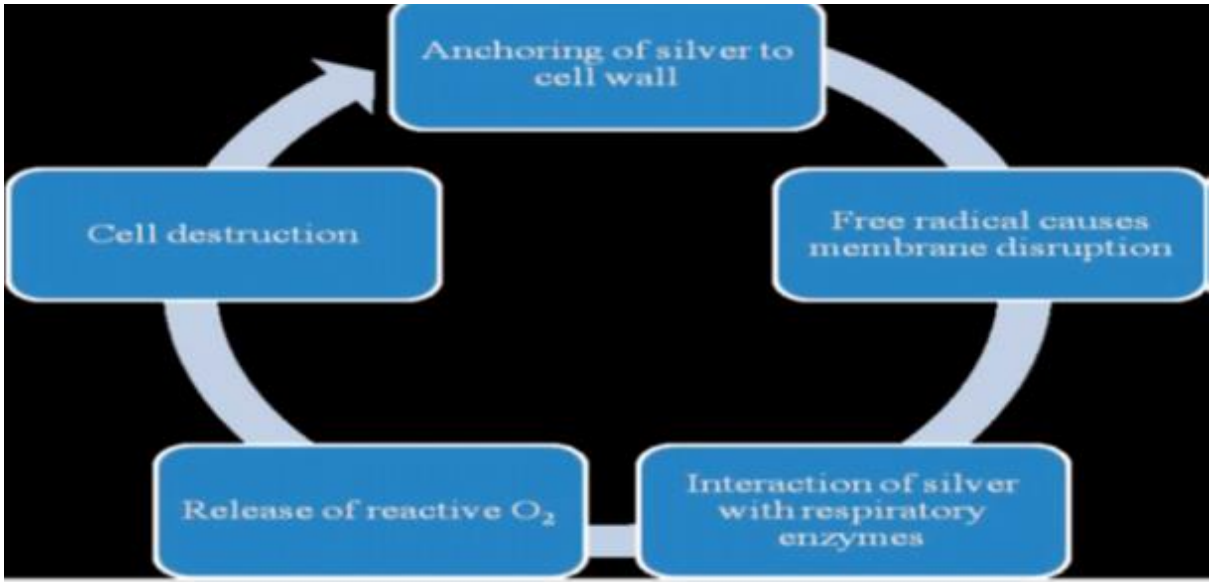
Antibacterial effect of siver nanaoparticles

In all over the countries many infectious diseases caused by pathogenic bacteria. These diseases causes different types of health risks and at least death of people[44].Due to the inceseacing of infectious diseases many countries are effected by their economy, social aspects and the world wide cost, which cannot be estimated. Most of the world wide public health problem causes by multi-resistance bacteria and new resistant strain of bacteria. These bacteria's frequently decreasing the efficacy of treatments leading to severe public health risks[34].Due to this reason the development of new antibiotics is possible by using the multi resistance bacteria. Silver nanoparticles (AgNPs) are the most hopeful nanoparticles now a days due to their large surface area to volume ratio and novel antibacterial and antiviral properties.[45].By analyzing the growth, morphology, and ultrastructure of the bacterial cells,(Staphylococcus aureus and Escherichia coli)were examined on the treatment with silver ion solution. These silver ion particles generated electrically and through investigated the antibacterial effect and mechanism of action of silver ion in different types of bacteria.

In 2012,53 strains were observed in different fungi by Devi and Joshi screened the mycosynthesis of AgNPs in different fungi and reported that the consequence effectiveness against S. aureus, Streptococcus pyogenes, Salmonella enterica and Enterococcus faecalis.[55]

Antibacterial mechanisms through direct contact with microorganisms

Silver nanoparticles have the ability to anchor to the bacterial cell wall and subsequently penetrate it, thereby causing structural changes in the cell membrane like the permeability of the cell membrane and death of the cell. There is formation of 'pits' on the cell surface, and there is accumulation of the nanoparticles on the cell surface.[25] .This action will cause physical changes in the bacterial membrane, like the membrane damage, which can lead to cellular contents leakage and bacterial death. It was also demonstrated that the antibacterial effect of AgNPs on Gram-negative bacteria was stronger than Gram-positive bacteria. This phenomenon can be explained by the existing difference in the cell wall thickness between Gram-positive bacteria (30 nm) and Gram-negative bacteria (3–4 nm), which are mainly composed of peptidoglycan[40] After adhesion to the bacterial wall, AgNPs can also penetrate the membrane and enter the bacteria. There is a size-dependent antibacterial effect, namely smaller nanoparticles has a large surface area in contact with the bacterial cells and can reach the cytoplasm more often than larger nanoparticles. When AgNPs penetrate inside the microbial cell, it may interact with cellular structures and biomolecules such as proteins, lipids, and DNA. Interaction between AgNPs and cellular structures or biomolecules will lead to bacterial dysfunction and finally death.[46-48]

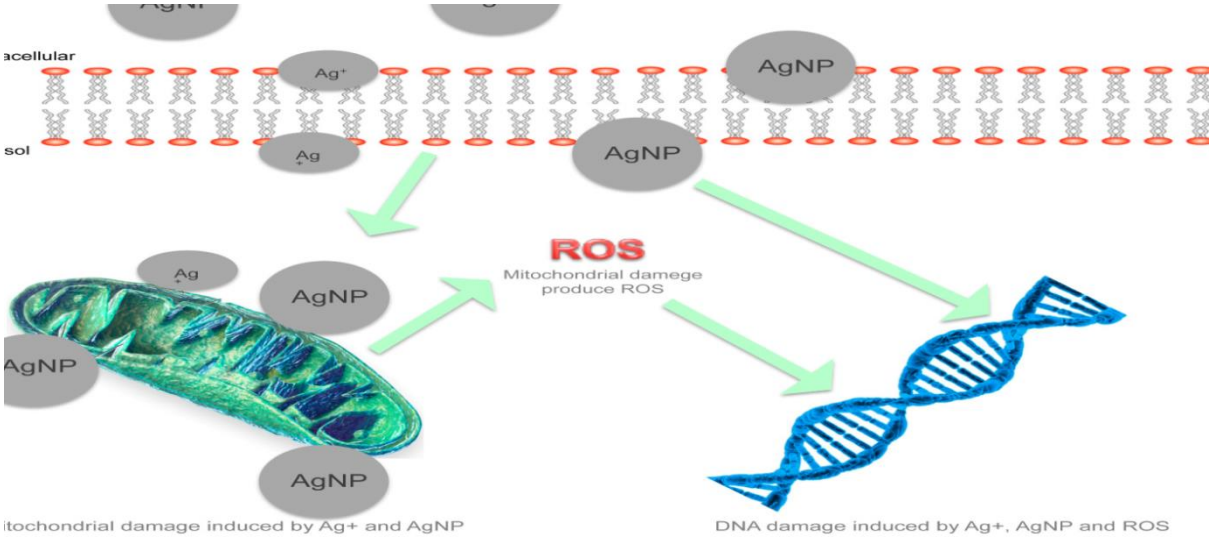


Mechanism of silver nanoparticles

Due to their ability of producing high levels of reactive oxygen species(ROS) and free radicals spices ,the another mechanism of AgNPs is used against bacteria or microorganisms.[49].

Durán et al,repoted the antibacterial activities, in central part of (E-Coli bacteria) on the action of silver nanoparticles. The silver ions bind easily to the protein and nucleic acid negatively charged compare than AgNPs.[21]. Due to binding of silver ions, the structure of bacterialcell and deformations in cell wall, in the membranes and in the nucleic acids of the bacterial cell of E-Coli is changed. Indeed, silver ions interact with a number of electron donor functional groups (such as thiols, phosphates, hydroxyls, imidazoles and indoles).[50].Silver ions or small AgNPs can easily enter the microbial body causing the damage of its intracellular structures. As a consequence ribosomes may be denatured with inhibition of protein synthesis, as well as translation and transcription can be blocked by the binding with the genetic material of the bacterial cell.[26].

ROS generated in cells is limited and can be eliminated by antioxidant system under normal situation. AgNPs exert antibacterial effect through inactivation of respiratory chain dehydrogenases and eventual excess ROS generation, which inhibited respiration and growth of cells. ROS generated in cells is limited and can be eliminated by antioxidant systems.AgNPs can reduce the quantity of cellular compounds (antioxidant enzyme) such as glutathione (GSH), superoxide dismutase, and catalase, which can accelerate the accumulation of ROS. Increased ROS lead to give harmful response, lipid peroxidation, and depletion of GSH, and DNA damage.[46,50]



Schematic representation of various cellular responses to AgNP induced toxicity mechanisms. In particular AgNPs induce mitochondrial and DNA damage by ROS Details of AgNPs and their mechanisms of action against bacteria and biofilms.

Bacteria	**Mechanism of Action**
Acinetobacter baumannii	Alteration of cell wall and cytoplasm
Escherichia coli	Alteration of membrane permeability and respiration
Klebsiella pneumoniae	Alteration of membrane
Nitrifying bacteria	inhibits respiratory activity
Pseudomonas aeruginosa	Irreversible damage on bacterial cells; Alteration of membrane permeability and respiration
Staphylococcus aureus	Irreversible damage on bacterial cells Inhibition of bacterial DNA replication, bacterial
Staphylococcus epidermidis	cytoplasm membranes damage, modification of intracellular ATP levels
Salmonella typhi	cytoplasm membranes damage, modification of intracellular ATP levels
Vibrio cholerae	Alteration of membrane permeability and respiration

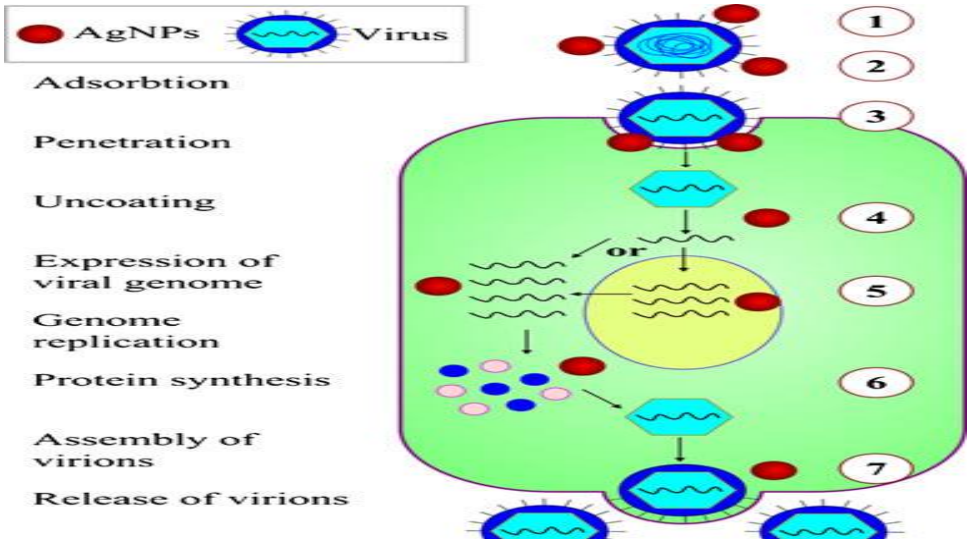
Antiviral effects of silver nanoparticles:

In the last few decades several viral diseases are appear due to increase in human populations ,human activities and pollution in the world. The SARS coronavirus, West Nile virus, monkey pox virus, Hantavirus, Nipah virus, Hendravirus, Chikungunya virus, the threat of pandemic influenza viruses, most recently of avian or swine origin are the examples of viral diseases[51].Similarly the action of antibacterial mechanism, the viral infections is governed by complex interactions between the virus and the host cellular system. All viruses depend upon a host cell for their protein synthesis. When virus enters the body firstly it bind to the

cell and then its genome enters in the cytoplasm. The genome is liberated from the protective capsid and, either in the nucleus or in the cytoplasm, it is transcribed and viral mRNA directs protein synthesis. Finally, the virus undergoes genome replication and together with viral structural proteins assembles new virions which are then released from the cell[52].

Elechiguerra et al.[53] were the first to describe the antiviral activity of metal nanoparticles. In their investiagation, they saw that the nanoparticle interactions with a

capping agent molecule.They repoted that the silver nanoparticles undergo size-dependent interactions with HIV-1.Silver nanoparticles have different physicochemical properties so that's why AgNPs tested with three different surfaces morality.1.Foamy cabon,2.poly N-vinyl-2-pyrrolidone(PVP) and 3 .bovine serum albumin(BSA). Foamy carbon-coated silver nanoparticles were incapsulated in a foamy carbon matrix needed to prevent the interfuse during their synthesis. PVP-coated nanoparticles were synthesized using glycerine as both reducing agent and solvent. In this method, a metal precursor is dissolved in a liquid polyol in the presence of a capping agent such as PVP[54]. The Synthesis in aqueous solution was deals for BSA-conjugate silver nanoparticles. In this synthesis **Elechiguerra et al**.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. The capacity of silver nanoparticles to inhibit infectivity of a laboratory-adapted HIV-1 strain at non-cytotoxic concentrations was determined by in vitro assays, and a dose-dependent inhibition of viral infectivity was reported.[52].



Mechanism of antiviral effect of AgNPs on different stages of virus replication: 1—interaction with viral surface, 2—interference with viral attachment, 3—inhibition of virus penetration into the cell, 4—interaction with viral genome, 5—inhibition of genome replication, 6—inhibition of protein synthesis, 7—inhibition of assembly and release of virions.

<u>Antifungal effects of silver nanoparticles:</u>

Antifungal activity of AgNPs is less studied compared to antibacterial activity,and anti viral activity [55]. Silver nanoparticles are being extensively synthesized using various

fungi[56] such as Fusarium oxysporum[57], Fusarium semitectum[58], Aspergillus fumigatus[59], Pleurotussojarcaju[60], Penicillium brevicompactum[61], Clostridium versicolor[62]. Sastryet al. [63] synthesized the silver nanoparticles intracellularly within the cell walls of Verticillium sp.

Vigneshwaran et al. [64,56] employed Aspergillusflavus to produce silver nanoparticles. the activity of chemically synthesized AgNPs against44 strains of six fungal species viz. Candida albicans, C.tropicalis, C. glabrata, C. parapsilosis, C. krusei and Trichophyton mentagrophytes studied by Kim et al. (2008) .**Candida sp. Jo et al. (2009)** studied the activity of both silver ions and nanoparticles against two plant-pathogenic fungi, Bipolaris sorokiniana and Magnaporthe grisea[66]. **Gajbhiye et al. (2009)[**67] reported effectiveness of biosynthesized silver nanoparticles against Phoma glomerata, P. herbarum, Fusarium semitectum, Trichoderma sp. and C. albicans. Further, they also reported the synergistic effects in combination with fluconazole[55].The remarkable antimicrobial activity of Ag NPs synthesized from Cryphonectria sp. against S.aureus, E. coli, Salmonella typhi and C. albicans, reported by **Dar et al.(2013)[**68] He said AgNPs can be used as potential antifungal agents.There are various reports on antifungal activity of AgNPs, a precise mechanism of such effect has not been reported. One of possible explanations is destruction of membrane integrity of fungi and inhibition of normal budding process in yeasts **(Kim et al. 2009)[**55,69]. **Lara et al. (2015)[**71-74] believed that AgNP attach and anchor to the surface of the fungus and produce an increase of reactive oxygen species (ROS).This interaction causes structural changes and damage, markedly disturbing vital cell functions, such as permeability and the membrane potential, forming pores causing ion leakage and other materials, depressing the activity of respiratory chain enzymes and, finally, leading to cell death.[70]

CONCLUSION:

Nanoparticles are supervene materials that have a broad range of applications and notable characteristics different from those of bulk materials. Silver nanoparticles(Ag-NPs or nanosilver) are one of the most widely used nanoparticles, which has antimicrobial properties for medical applications. The toxicity of nano silver may be explained by the interaction of nanoparticles with microbes involving silver ion release and particle cellular internalization.3,4 Size dependent toxicity of nanosilver supports the mode of action of Ag-NPs. AgNPs have the ability to interact with various microorganisms (such as bacteria) and also impact both the growth of and mature

bacterial biofilms and, therefore, could be used as broad spectrum antimicrobials. The antibacterial effect appears to be conferred by their ultra-small size and increased surface area, through which they destroy the membrane, cross the body of the microbe and create intracellular damage. Due to the structural difference in the composition of the cell walls of Gram-positive and Gram-negative AgNPs have significantly less effect on the growth of Gram-positive bacteria. It is now clear that AgNPs possess a strong antibacterial and antiviral activity, highlighted by several studies .Several research has shown that the functionalization immobilization and/or hybridization of NPs can enhance and improve the antimicrobial activities of the nanomaterials against a wide range of multi-resistant strains of pathogenic microorganisms. Generally, most nano particles antimicrobial drugs were able to target and transit difficult membrane barriers, deliver and sustain the NP antimicrobial doses resulting in disease clearance which is a difficult phenomenon for conventional antimicrobials.

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