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Review Article

REVIEW ON SILVER NANOPARTICLE GEL FOR EFFECTIVE ANTIMICROBIAL EFFECT

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ABSTRACT

Antibiotic resistance is spreading among many harmful microorganisms. Recovering from multidrug-resistant (MDR) infections is a challenging matter that necessitates several treatments using broad-spectrum antibiotics, which are more costly, hazardous, and less effective. The strong antibacterial and anti-biofilm properties of silver nanoparticles (AgNPs) are drawing a lot of interest. According to their properties, the combination of AgNPs with hydrogels increases the antibacterial activity; the hydrogels effectively stabilize the AgNPs and regulate their release. This review discusses about the microbial infection, role of silver, formulation and evaluation of AgNP, reported AgNP loaded gel with its uses. Moreover, the proposed AgNPs gel can show prolonged antimicrobial efficiency, making it eligible as a treatment agent for infectious wounds in animals.

Keywords: Antimicrobial, AgNP, silver, Nanotechnology, Plant extracts, Green synthesis

INTRODUCTION

Infectious diseases resulting from pathogenic microorganisms represent a persistent health risk in every nation and are among the leading causes of death globally. The impact of infectious diseases on health, the economy, and other facets of society is so multifaceted nowadays that it is impossible to calculate the whole cost globally. The restricted diversity, antagonistic interactions, and consequences of incomplete antibiotic treatments that lead to the development of microorganism resistance are just a few of the serious drawbacks of current antimicrobial medicines (Done and Halden, 2015).

One of the biggest global public health issues is multi-resistant bacteria, and when new resistant strains emerge on a regular basis, the effectiveness of existing therapies is diminished, posing a serious risk to public health. It also has a deleterious effect on a number of human endeavors, including veterinary care, aquaculture, and agriculture. Unfortunately, the rate at which new antibiotics are developed has been surpassed by the evolution of multi-resistant bacteria; for this reason, the development of novel and effective antimicrobial treatments is essential (Paphitou, 2013; Cassell, 2001).

The use of metals as antimicrobial agents has proven to have strong scientific evidence since antiquity, based on the evidence of the microcidal lethal effects of essential metals (indispensible for the biochemistry of life in all organism fulfilling cellular functions) in excess dose and nonessential metals even at

very minute doses. In some instances, the biocidal action of antibiotics (such as bacitracin, bleomycin, streptonigrin, and albomycin) is regulated by metal ions that are tightly bound to their structure. In other cases, antibiotic molecules (such as tetracyclines, aureolic acids, and quinolones) have metal ions attached to them that improve their activity without significantly altering their structure. Researchers and nanotechnologists were very interested in the creation of metal nanoparticles because of their microcidal properties. Green synthetic nanoscale objects containing various metals such as copper, zinc, titanium, magnesium, gold, and silver are being created. However, the synthesis of silver nanoparticles using a green method has potential applications in the biomedical field, particularly in the development of antimicrobials. Other green synthesized metals, such as gold, find numerous applications in various fields of engineering and technology due to their low-dimensional structure (AgNPs) (Roy *et al*., 2019; Lemire *et al*., 201).

Silver: an effective antibacterial agent

Since a wide range of tiny organisms have been shown to be poisonous to silver (Ag), silver-based combinations have been extensively used in antibacterial applications. As bactericidal agents, a few salt forms of Ag and their subclasses are commercially useful. Silver particles have a very noteworthy bactericidal effect on microorganisms; in any event, the bactericidal system is still not fully understood. According to reports, Ag+ ions form a strong bond with the thiol (-SH) linkages of essential chemicals, effectively disabling them. Experiments have demonstrated that when Ag-based particles are applied to microorganisms, the DNA's ability to replicate is lost. Various assessments have confirmed fundamental changes in the cell layer and the distribution of small electron-thick granules formed by sulfur and silver (Gupta and Silver, 1998 Feng *et al*., 2000)

In order to create new materials and products, the discipline of nanotechnology works with materials that have at least one dimension in the range of 1 nanometer to 100 nm. Because of their exceptional, superior, and necessary qualities, nanomaterials differ greatly from macroscopic materials. Because of their unique qualities, nanomaterials have recently attracted attention from researchers. Their high surface-to-volume ratio and more atoms in the grain boundaries are two of the main distinctions. Owing to their special characteristics, nanomaterials play a key role in the creation of novel gadgets that have applications in a wide range of industries, including biomedicine, physics, medicine, pharmacy, and cosmetics. Lately, nanotechnology has demonstrated significant promise and effective outcomes in the treatment of bacterial illnesses (Crisan *et al*., 2021; Annamalai and Nallamuthu, 2016).

Antibacterial Mechanism of Silver Nanoparticles

Numerous antibacterial activities have been postulated for silver nanoparticles, despite the fact that the precise mechanism behind these effects is still unclear. One theory about how to kill microorganisms is that silver nanoparticles can continuously discharge silver ions. Silver ions have an affinity for sulfur proteins and electrostatic attraction, which allows them to stick to the cytoplasmic membrane and cell wall.

The bacterial envelope may be disrupted as a result of the adhering ions' increased cytoplasmic membrane permeability. Respiratory enzymes can become inactive following the uptake of free silver ions into cells, which produces reactive oxygen species but halts the synthesis of adenosine triphosphate. Reactive oxygen species have the potential to be a major cause of DNA alteration and disruption of cell membranes. Due to the fact that phosphorus and sulfur are essential parts of DNA, interactions between silver ions and these elements can disrupt DNA replication, impair cell division, or even cause the microorganisms to die. Furthermore, by denaturing ribosomes in the cytoplasm, silver ions can prevent the creation of new proteins (Ramkumar *et al*., 2017; Durán *et al*., 2016).

Approaches for AgNP synthesis

Physical methods

In physical processes, evaporation-condensation is typically used to create metal nanoparticles; this process can be done in a tube furnace at room pressure. A carrier gas is created when the source material inside a boat centered at the furnace evaporates. Using the evaporation/condensation method, nanoparticles of many materials, including Ag, Au, PbS, and fullerene, have been created in the past. A tube furnace takes up a lot of room, uses a lot of energy to raise the temperature surrounding the source material, and takes a long time to reach thermal stability, which are some of the disadvantages of producing silver nanoparticles (AgNPs) using a tube furnace. A typical tube furnace needs many tens of minutes to preheat and requires power usage of more than several kilowatts (Kruis *et al*., 2000; Magnusson *et al*., 1999).

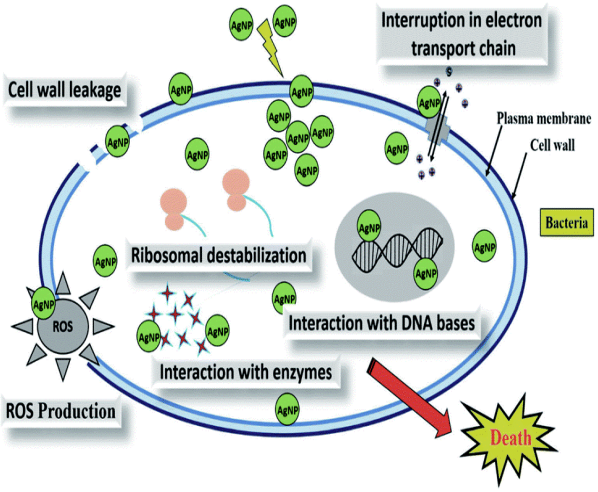

Figure 1: Pictorial representation of mechanism action of AgNP

Chemical methods

The most widely used technique for producing stable, colloidal dispersions of AgNPs in water or organic solvents is chemical reduction. Citrate is the most often used reductant. Silver is reduced in an aqueous solution, producing colloidal silver ions that are nanoscale. Any colloidal dispersion must be stable, which can be accomplished by adding a stabilizing agent (dodecanethiol) to the surface, which will adsorbe and create a protective coating. It can prevent the system from clumping together and growing crystallized. AgNPs undergo significant variations in size, shape, morphology, polydispersibility index, self-assembly, and zeta potential (stability) as a result of minute adjustments made to the polymers. Polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG), glycol derivatives, are commonly utilized components in the synthesis of AgNPs and AuNPs. When synthesizing AuNPs, polyacrylamide serves as both a stabilizing and a reducing agent.

Surfactants with functional groups like amines, thoils, and acids are crucial for maintaining the stability of colloidal dispersion, which shields the system against agglomeration, coaleseces, and crystal formation. Nowadays, saccharides, silver hydrosols, and reducing agents are used to create AuNPs created by the modified tollens method, producing AgNPs in the range of 20–50 nm and 50–200 nm, respectively (Oliveira *et al*., 2005; Yin *et al*., 2002).

Biological approaches

One new method for creating biological AgNP synthesis is biotechnology. In addition, because of their increased surface area, magnetic nanoparticles have a significant deal of antibacterial potential in treating elevated microbial resistance to a variety of drugs and antibiotics. Green chemistry is now a fast-growing method for producing AgNPs without harmful side effects by using naturally occurring stabilizing, reducing, and capping agents. It has been effectively documented that the combined use of herbs and specific proteins, microbes, bacteria, fungus, and enzymes in biological synthesis can reduce metal ions (Iravani, 2011; Mohanpuria *et al*., 2008).

Characterization of AgNP

FTIR analysis

An investigative method for identifying or confirming the functional groups present in the moiety that are indicative of that molecule is FTIR spectroscopy. The primary functional components of AgNPs and the herbal extract were detected by scanning the samples between 4000 and 400 cm−1 (Singh *et al*., 2013).

SEM/TEM analysis

The primary application of transmission electron microscopy and scanning electron microscopy is the investigation of the surface morphology of produced AgNPs. Silver nitrate was added to SEM/TEM plates in order to create a solution smear on slides. By creating a thin layer of platinum and coating slides in it, conductivity was added to the system. When the slides were prepared, they were scanned at an accelerating voltage of 20 KV, producing high-quality images (Kathireswari *et al*., 2014).

Visual and UV: Visible study

Using a UV-visible spectrophotometer, samples' visual and calorimetric appearances were examined before and after AgNP formulation at various time intervals to determine whether or not AgNPs had formed. Silver nitrate is colorless prior to AgNP production, whereas herbal extract has a distinct color. After interacting with the herbal extract, AgNPs-synthesised silver nitrate solution takes on a yellowish brown color, as demonstrated by surface Plasmon resonance SPR and UV visible absorption in the 400–475 nm wavelength range (Kumar, 2014).

X-ray diffraction (XRD) analysis

A recent method called X-ray diffraction is primarily used to determine the condition of matter at various radiation angles, whether it is crystalline or amorphous. Cell dimension and phase (crystalline/amorphous) are determined by X-ray diffraction (Shoib and Shahid, 2014).

AgNP loaded gel

Lately, numerous writers and investigators have taken an interest in gels. Three-dimensional cross-linked polymer networks, or hydrogels, are intelligent enough to

respond to changes in their surroundings (such as pH, temperature, ionic strength, electric field, enzyme presence, etc.) and swell or shrink appropriately without dissolving and creating colloidal suspension. When swelled, they have a rubbery, squishy texture that mimics real tissue and has good biocompatibility. As a result, hydrogels are widely used in a variety of pharmaceutical and biomedical engineering applications, such as controlled release drug delivery systems, antibacterial factor, and tissue engineering (Un Nabi *et al.,* 2016).

Gels can be classified into several categories depending on

- Source (natural or synthetic),
- Configurations (non-crystalline, semicrystalline and crystalline), type of crosslinking (chemical or physical interaction),
- Physical appearance (matrix, film or microsphere)
- Network electrical charge (neutral, ionic, amphoteric electrolyte or Zwitterionic).

Furthermore, hydrogels can be divided into four groups according to their preparation techniques: copolymers, homo-polymers, semi-interpenetrating networks, and interpenetrating networks. While copolymer hydrogels are created by cross-linking two co-monomer units—at least one of which needs to be hydrophilic in order for the hydrogels to swell—homopolymer hydrogels are cross-linked networks of a single kind of hydrophilic monomer unit. Hydrogels that are semi-interpenetrating are created when a linear polymer enters a cross-linked network and stays there without forming further chemical connections (Rehman and Zulfakar, 2014).

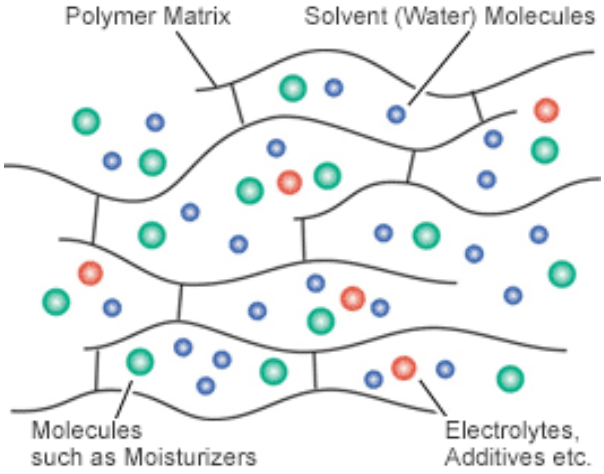

Figure 3: Internal structure of gel

Evaluation of gel

Physical examination and pH measurement

It is important to physically inspect the semi-solid formulations to ensure that they are uniform in color and consistency. Additionally, the pH was assessed again (before to each usage) to ensure that it remains stable at the skin's pH of 5.5.

Rheological evaluation

A Brookfield viscometer is used to measure the prepared hydrogels' viscosity. Because the formulations are viscous, their viscosities can be found by dissolving 1, 3, and 5 g of the semi-solid formulations in 25 ml of pure water for 24 hours (Aiyalu *et al*., 2016).

In-vitro drug diffusion study

Franz diffusion cell used cellophane membrane as a barrier to study drug diffusion rates from various gel compositions. The diffusion membrane is submerged in the receptor compartment, which has a diffusion medium of ethanol:water (1:1) and is kept at 370C for 24 hours to achieve equilibrium. The diffusion membrane that divides the donor and receptor compartments should be combined with the diffusion cell on a

magnetic stirrer. Gel (2g) needs to be maintained on the membrane within the donor compartment. The contents must be agitated using magnetic stirrer at 50 rpm and aliquots each of 5 ml should be removed from the release medium at time intervals of 10, 20, 30, 60, 90, 120,180, 240, 300, 360, 420 and 480 minutes. Equal amounts of the same fresh medium must be used to replace the removed samples. These samples' absorbance should be measured spectrophotometrically (Shirsand *et al*., 2012).

Drug content analysis

A little over 0.5 g of hydrogel needs to dissolve in 10 ml of water, be centrifuged for 30 minutes at 1000 rpm, filtered through Whatman No. 1 filter paper, sufficiently diluted, and have the extract concentration measured spectrophotometrically.

Extrudability

To determine how much force is needed to extrude hydrogel or any other semisolid preparation from a tube, this empirical test is helpful. Extrudability measurement becomes crucial as the formulation's packaging directly affects the amount of gels that are delivered from jars and tubes in the appropriate amount. This test can be performed with the Pfizer hardness tester. An aluminum tube was first obtained, and 15 grams of gel were weighed and placed inside. The amount of extruded gel was then weighed after 30 seconds of 1 kg/cm2 pressure. It is possible to calculate the percentage of gel extruded, and grades should be assigned in accordance (Bankar and Dole2016).

Spreadibility

The spreadibility test needs to be run with a glass slide and wooden block apparatus. The glass slide needs to be glued to the wooden block's surface before 2g of the prepared hydrogel is added to it. Gel is sandwiched between two glass slides, one of which has a hook. For five minutes, a 100 g weight is applied to the upper slide in order to release trapped air and create a consistent, thin gel layer in between slides. After removing the weight, the extra gel around the borders is scraped off. Slides are now securely fastened to a platform so that only the upper slide is able to move or slip off without interference due to the power of the weight attached to it. Carefully, a 20 g weight is fastened to the upper slide. To determine spreadibility, one must record the amount of time it takes the upper, moveable slide to move 6 cm and separate from the bottom, fixed slide in the weight's direction (Yadav *et al*., 2010).

Determination of antimicrobial activity

The well diffusion method can be used to examine the hydrogels' antibacterial activity. This technique is based on the antimicrobial agent diffusing from holes punched in the agar that has been seeded with microbes. Every bacterial isolate is seeded onto agar plates that have been prepared in accordance with the manufacturer's instructions. After allowing the agar plates to set, the seeded agar media is punctured using a sterile cork borer (8 mm in diameter). A certain volume of hydrogels is utilized to fill the holes using a sterile instrument. Before being incubated for 48 hours at 25 ± 1°C, the plates are allowed to stand at room temperature for 15 minutes to allow for prediffusion. Following incubation, growth is assessed, and measurements of each inhibitory zone's diameter should be made (Patel and Patel, 2015).

Positive outcomes of Gel loaded with AgNP

AgNPs are added to hydrogels to increase their antibacterial activity and modify their swelling ratio, mechanical toughness, and stimulus responsiveness. Based on their properties, gels have the potential to function as an effective AgNP stabilizer and regulate AgNP release. As long as the connections between the polymer and the nanoparticles are minimal, adding metal nanoparticles to the resulting nanocomposite hydrogels has no effect on their mechanical properties (Hoiby *et al*., 2011).

Ag-NPs attach themselves non-specifically to bacterial membranes and other substances, causing structural alterations that worsen mitochondrial dysfunction and increase membrane permeability. Therefore, to maintain antibacterial activity by hydrogel composites with optimized properties for biomedical use, regulated release of AgNPs is required. AgNPs released under controlled conditions offer continuous protection for a while without requiring the removal of wound dressings (Ito *et al*., 2009; Hobman and Crossman, 2014).

CONCLUSION

AgNPs may be able to fight germs in humans and animals that are infected. AgNPs' biological activity is largely dependent on their form and size. AgNPs gel may have potential applications as a substitute antimicrobial agent. The incorporation of AgNP into the gel allows for the sustained release of AgNPs, which can be beneficial in killing bacteria. Furthermore, the suggested AgNPs gel demonstrated sustained antibacterial efficacy, qualifying it as a therapeutic agent for animal infections wounds. Additionally, by confirming the efficacy of the AgNPs loaded gel in clinical trials, this opens the door for further research.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

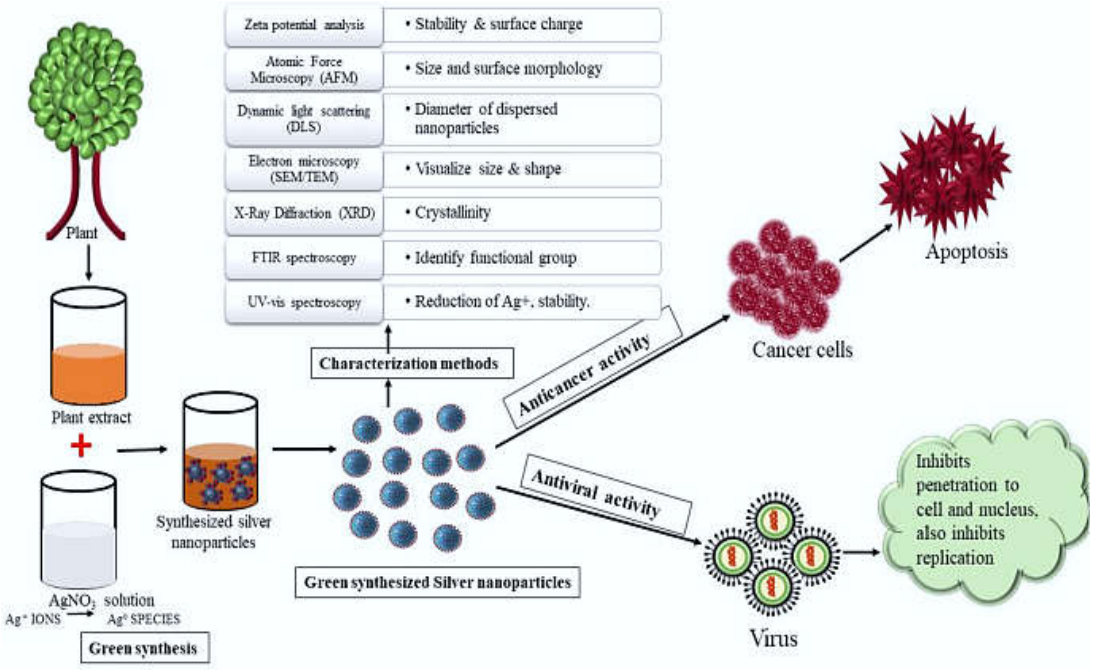

Figure 2: Overview of preparation, characterization and usage of AgNP

Table 1: Previously reported studies of green synthesised AgNP gel

Name of plant used	Application	Reference
Ammania baccifera	To treat infections associated with burns.	(Jadhav *et al*., 2016)
Chrysanthemum morifolium	Provided a clinical ultrasound gel with bactericidal property for prevention of cross infections.	(He *et al*., 2013)
Aloe vera	Antimicrobial effect	(Logaranjan *et al*., 2016)
Pongamia pinnata	Treating topical infections especially in wounds.	(Paul and Londhe, 2019)
Tridax procumbens	In treating wound healing	(Fatima *et al*., 2021)
Vaccinium subg. Oxycoccus	Antimicrobial activity	(Ashour *et al*., 2015)
Schinus terebinthifolius Raddi	To enhance microbial inhibition	(de Oliveira *et al*., 2021)
Ganoderma applanatum	Skin antibacterial	(Maneewattanapinyo *et al*., 2023)
Agrimonia eupatoria	For wound healing	(Balazova *et al*., 2023)
Potentilla fulgens	For wound healing	(Bharali *et al*., 2023)
Manilkara zapota	For treating pathogenic infections	(Parashar and Garg, 2023)
Verbascum Longipedicellatum	For inhibiting bacteria and fungi growth	(Kıvanc, 2022)
Woodfordia fruticosa	For purpose of ameliorating wound healing.	(Singh and Maheshwari, 2023)

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