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Silver Nanoparticles as a New Approach to Wound Healing: Focus on Antibacterial Efficacy

Berfin Rumeysa SARI[1], Cigdem AYDIN ACAR[1,2*]

1 Department of Health and Biomedical Sciences, Burdur Mehmet Akif Ersoy University, Burdur, Turkey

2 Department of Nursing, Burdur Mehmet Akif Ersoy University, Bucak School of Health, Burdur, Turkey

REVIEW ARTICLE

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ORCID:
Berfin Rumeysa Sarı: 0000-0002-1747-4785
Cigdem Aydin Acar: 0000-0002-1311-2314

*Correspondence: Cigdem AYDIN ACAR
Address: Burdur Mehmet Akif Ersoy University, Bucak School of Health, Department of Nursing, Burdur, Turkey
e-mail: cacar@mehmetakif.edu.tr
GSM: +90 248 213 82 75

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ABSTRACT

Nanotechnology is a multidisciplinary field that brings together researchers from various scientific disciplines, including biology, chemistry, materials science, and physics, to develop advanced functional materials on a nanoscale. Nanotechnology-based solutions, particularly nanoparticles, are becoming increasingly prevalent in medical research due to their significant advantages in both efficacy and safety compared to conventional therapies and diagnostic methods. Recent studies have shown that silver nanoparticles are highly potent antimicrobial agents against infectious organisms such as Escherichia coli, Bacillus subtilis, Vibrio cholera, Pseudomonas aeruginosa, Syphillis typhus, and Staphylococcus aureus. This broad antibacterial activity of silver nanoparticles has influenced the use of silver in medicine and expanded the applications of silver nanoparticles across various fields of biomedicine. Biomedical products containing AgNPs are typically used to accelerate wound healing and prevent bacterial infections by inhibiting bacteria through the rapid breakdown of infected cells. This study focuses on the antibacterial mechanism of silver nanoparticles and their effect on wound healing.

Keywords: Antibacterial, Silver nanoparticles, Nanotechnology, Wound healing

INTRODUCTION

Silver has been observed to aid wound healing since 69 BCE, and various medicinal applications of silver properties have been distinguished throughout history. While metallic silver (Ag) itself does not possess therapeutic applications, other forms such as silver ions (Ag^+) and nanoparticles exhibit a broad spectrum of antibacterial activity. These forms are cytotoxic to a range of bacteria, viruses, fungi, and even yeast, which may interfere with the wound healing process (Toczek et al., 2022). In modern medicine, silver is frequently employed in the form of silver nanoparticles (AgNPs) due to its physicochemical properties (Rybka et al., 2022). The advancement of nanoparticles has transformed the use of silver in medicine and broadened the applications of silver nanoparticles across various biomedical fields (Figure 1) (Pal et al., 2007; Veeraraghavan et al., 2021).

Silver Nanoparticles

Silver nanoparticles rank among the top ten nanoparticles produced globally and are recognized for their antibacterial, antifungal, cytotoxic, and phytotoxic properties (Kruszka et al., 2020). Recently, silver nanoparticles have been extensively researched due to their superior physical, chemical, and biological properties, with studies indicating that the advantages of AgNPs over bulk forms arise from their size, shape, composition, crystallinity, and structure (Lee and Hyun, 2019).

Silver nanoparticles possess a diameter not exceeding 100 nm and consist of approximately 20 to 15,000 atoms. The unique design of the Ag crystal unit cell (a cube with four Ag atoms) enables oxygen adsorption, which can be released into the environment (Kowalczyk et al., 2021). Studies demonstrate that reducing particle size alters the electronic structure of AgNPs and enhances their antibacterial activity.

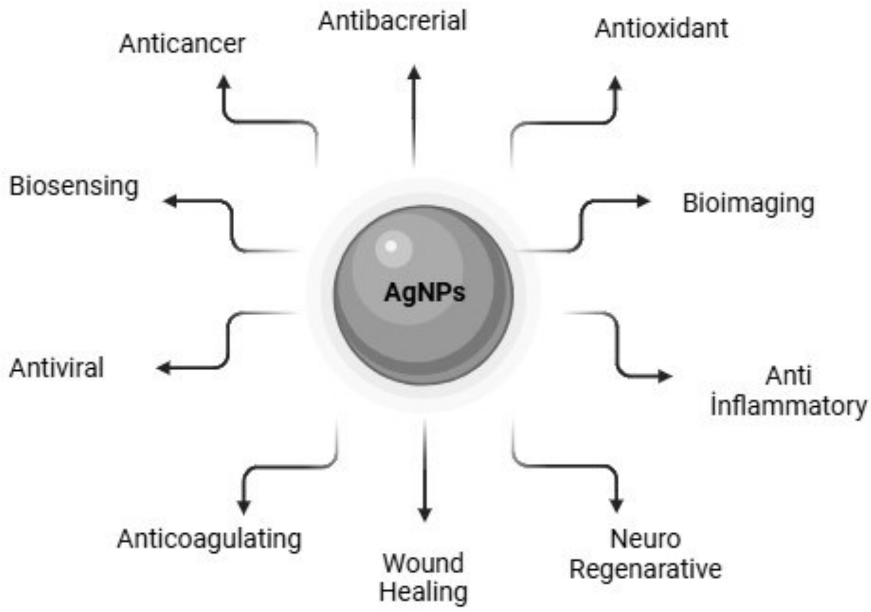

Figure 1: Application Areas of Silver Nanoparticles

Synthesis of Silver Nanoparticles

Numerous studies focus on the synthesis of AgNPs with controlled size and shape, and various specific synthesis methods have been developed, including physical, chemical, and biological methods (Xu et al., 2021). Generally, the formation of silver nanoparticles is associated with either a "bottom-up" or "top down" approach. As the term implies, in the "bottom-up" approach, smaller atoms or molecules assemble to form nanoparticles. Conversely, the "top-down" approach involves breaking down bulk materials into finer dimensions. In this process, nanoparticles are synthesized by using various lithographic techniques, such as milling, grinding, spraying, and thermal/laser ablation, to achieve the desired dimensions (Chung et al., 2021).

Chemical Synthesis of Silver Nanoparticles (Chemical Reduction)

Chemical reduction is one of the common methods and requires a reducing agent to convert silver ions into AgNPs. Common reducing agents, such as ascorbic acid, sodium borohydride, and block copolymers, play a role in stabilizing AgNPs (Nie et al., 2023). The chemical synthesis of nanoparticles is a bottom-up technique since the particles are composed of collective atoms within a nucleus rather than bulk material (Kaabipour and Hemmati, 2021). The use of toxic chemicals in the chemical synthesis method is a major concern due to its adverse effects on the environment and living organisms (Sharma et al., 2022).

Physical Synthesis of Silver Nanoparticles

Physical methods for preparing silver nanoparticles include evaporation-condensation and laser ablation. Advantages of physical methods include speed, the use of radiation as a reducing agent, and the absence of hazardous chemicals. However, disadvantages include low efficiency, high energy consumption, solvent contamination, and difficulties in achieving a homogeneous distribution (Rahuman et al., 2022).

Green Synthesis (Biological Synthesis) of Silver Nanoparticles

The need for the creation of ecologically friendly synthetic processes is increasing due to a number of drawbacks with the physical and chemical synthesis of nanomaterials. Green synthesis of AgNPs, a crucial area of nanotechnology, is developing (Nie et al., 2023). In recent years, green synthesis has opened a new avenue for creating AgNPs of various sizes and shapes without using toxic reducing agents and stabilizers. Green synthesis has advantages over chemical and physical methods, including being eco-friendly, cost-effective, natural, and easy to scale up for large-scale nanoparticle production. In biological synthesis, bacteria, plant extracts, fungi, and algae can be used as reducing agents and stabilizers (Liao vd., 2019). The green synthesis method of nanoparticles is shown in Figure 2.

Antibacterial Activity of Silver Nanoparticles

The antibacterial activity of AgNPs has been shown to result from the oxidation of released silver atoms and the release of Ag^+ ions from the surface of AgNPs. This feature is associated with the slow release and oxidation of Ag+ in a biological environment. In addition to Ag+'s capacity to penetrate cell membranes, it also affects cell division, directly leading to the death of the microorganism (Diniz et al., 2020; Mousavi et al., 2018). The bactericidal effect of AgNPs has been proposed to be linked to the direct contact of nanoparticles with the bacterial cell wall, followed by penetration into the cytoplasm. Direct contact of AgNPs with large surface areas on a bacterial cell wall can lead to membrane damage, causing leakage of cell contents and ultimately cell death (Liao et al., 2019).

widely used for antibacterial and antitumor activities and are also applied to accelerate the wound healing process (Fatima et al., 2021). Incorporating AgNPs into wound dressings has been shown to reduce infection rates and accelerate healing in chronic wounds such as diabetic ulcers and burns, offering hope to patients with hard-to-treat wounds (Jangid et al., 2024). Biomedical products with AgNPs are typically employed to promote wound healing and prevent bacterial infections through rapid breakdown of infected cells (Liao et al., 2019). The destruction of the bacterial cell wall by silver nanoparticles is shown in Figure 3.

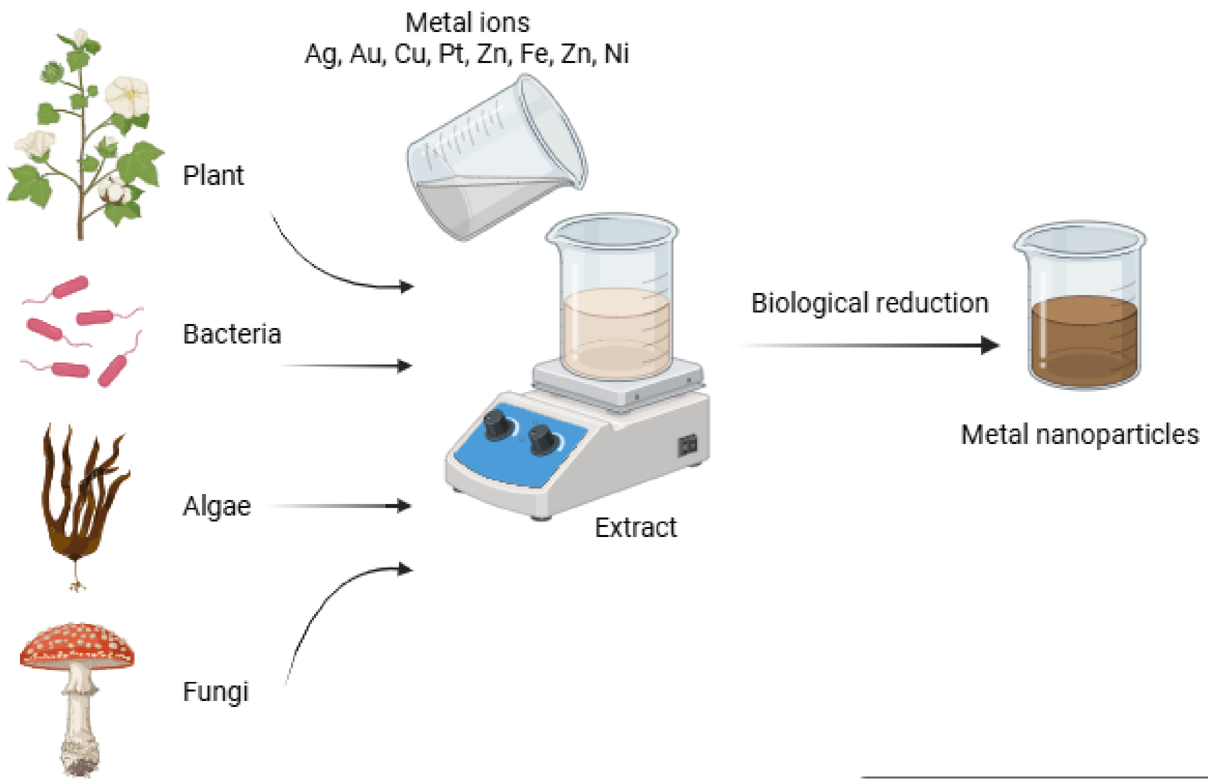

Figure 2: Nanoparticles Green-Synthesized by Plants, Bacteria, Fungi, and Algae (Aydin Acar, C. (2024) BioRender)

Although the exact mechanism of the antibacterial effects of silver nanoparticles is not fully understood, various antibacterial effects have been proposed (Yin et al., 2020). Previous studies have shown that nano-sized particles induce cytotoxicity by generating reactive oxygen species (ROS) or by increasing intracellular oxidative stress, triggering cell death processes involving apoptosis and necrosis (Mousavi et al., 2018). Nanoparticles act as antibacterials due to their ability to produce ROS. It is hypothesized that ROS are produced by the cell as the first line of microbial defense (Awad et al., 2021). Reactive oxygen species are fundamental agents in the provocation of cell membrane degradation and DNA modification. Since sulfur and phosphorus are key components of DNA, the interaction of silver ions with sulfur and phosphorus in DNA can lead to problems in DNA replication and cell proliferation, and even result in the eradication of microorganisms. Additionally, silver ions may inhibit protein synthesis by denaturing ribosomes in the cytoplasm (Singh et al., 2022; Prabhu and Poulose., 2012; Yin et al., 2020).

Silver nanoparticles possess excellent antibacterial properties, damaging the structure of the bacterial cell membrane and ultimately inducing apoptosis. AgNPs are

Wound Healing Properties of Silver Nanoparticles

The four stages of wound healing include hemostasis, inflammation, proliferation (new tissue formation, granulation, and angiogenesis), and tissue remodeling; these stages may overlap in time and space. Following initial hemostasis, inflammation is a critical part of the normal wound healing process. Wound healing is one of the primary survival mechanisms, relying on a highly complex series of biological events or processes. However, these mechanisms can be compromised by multidrug-resistant (MDR) microorganisms that prolong inflammation, as they inhibit epithelialization and cellular processes, potentially leading to a chronic wound (Dutt et al., 2023). Extracellular bioengineered AgNPs under optimized conditions can serve as a powerful weapon against multidrug-resistant bacterial pathogens (Gaikwad et al., 2022). Today, antibacterial AgNPs have the potential to serve as alternatives to current antibiotics due to increasing bacterial resistance (Kaabipour and Hemmati, 2021).

AgNPs possess a large surface area, which allows for the release of significant amounts of silver ions and the potential to penetrate the skin, particularly damaged skin. Numerous reports indicate that AgNPs support wound healing and exhibit antibacterial properties against a broad spectrum of bacteria, including Pseudomonas aeruginosa, Escherichia coli, and Staphylococcus aureus (Orlowski et al., 2018). In a study conducted by Erdem and Acar, it was observed that Cv-SeNPs synthesized via the green synthesis method were effective against E. faecalis, S. aureus, and E. coli bacteria. At a concentration of 1500 µg/mL, the antibacterial inhibition zone diameters against the three pathogenic microbes were observed to be 12.13 mm, 10.14 mm, and 10.09 mm, respectively (Erdem and Acar, 2024).

AgNPs are primarily used as therapeutic agents for wound healing purposes due to their notable anti-inflammatory and antibacterial properties. When AgNPs come into contact with the affected area, they initiate neutrophil apoptosis by reducing mitochondrial membrane potential, which subsequently lowers cytokine production. Consequently, this modulates or reduces the inflammatory response, leading to faster healing (Nqakala et al., 2021).

provide a moist environment conducive to recovery (Shi et al., 2020). Compared to traditional wound healing, agents like metal and metal oxide nanomaterials are more appropriate due to their superior intrinsic qualities, such as catalytic, optical, and melting properties (Singh et al., 2022). Many nanoparticles themselves serve as intrinsic therapeutic agents; for example, AgNPs exhibit broad-spectrum antibacterial properties against fungi and bacteria, including antibiotic-resistant strains. They are now widely used in biomedical applications for wound dressing and management (Bhubhanil et al., 2021).

There are two primary models for studying wound healing: in vitro and in vivo models. In vivo studies provide direct analysis of a stimulus on a living subject before, during, and after exposure (Younis et al., 2022). Vijayakumar et al. examined the in vitro scratch wound healing activity of AgNPs synthesized via green synthesis using probiotic bacteria. The study observed a 96% wound healing efficiency in injured cells exposed to AgNPs for 72

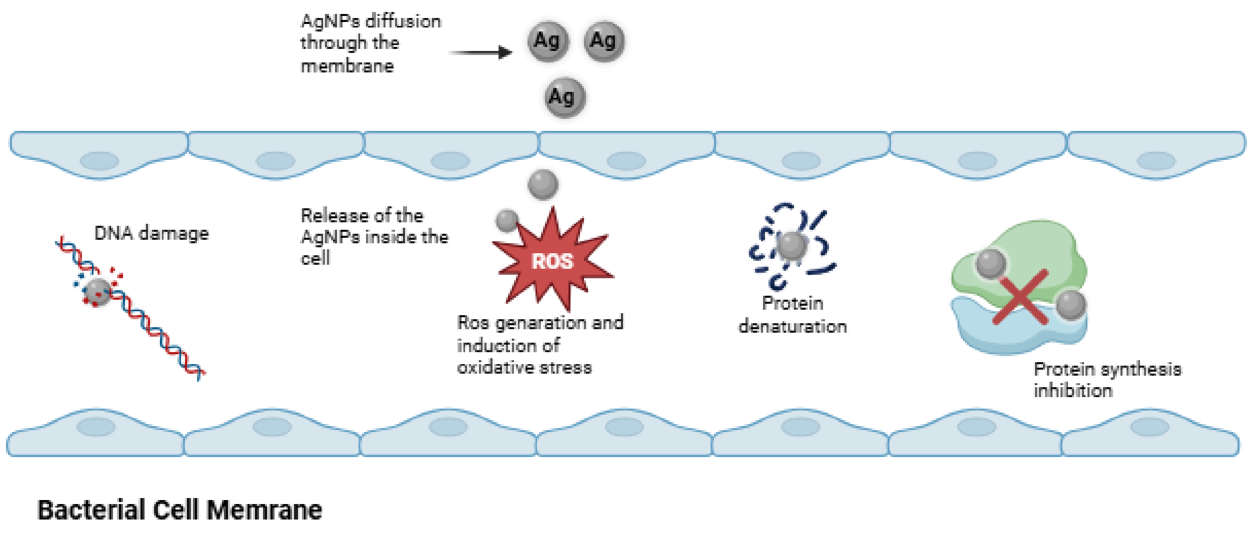

Figure 3: Mechanism of Bacterial Degradation by Silver Nanoparticles Passing Through The Bacterial Cell Wall

Silver Nanoparticles and Wound Dressing

Wound dressings have been identified as the most advanced technique for treating various skin injuries related to thermal or physical damage (Thanh et al., 2018). For wound healing, a dressing should be able to maintain a stable temperature, support the healing process, protect new cells, and exhibit antibacterial activity (Diniz et al., 2020). Traditional dressings, also referred to as inert dressings (such as gauze, cotton pads, and bandages), are the most widely used clinical dressings due to their low cost and simple manufacturing processes. However, challenges in maintaining a moist wound environment and their tendency to adhere to granulation tissue limit their applications. Modern dressings may be more suitable candidates for wound healing due to their ability to

hours (Vijayakumar et al., 2023). In another in vitro study, in a Cell Migration Assay (Scratch Test) study, Shehabeldine et al. demonstrated that silver nanoparticles prepared with chitosan support wound healing, reduce infection, and decrease the risk of silver absorption (Shehabeldine et al. 2022). In vitro studies are generally the first step in validating the efficacy of a wound product. Since laboratory test conditions differ significantly from the human wound environment, the extrapolation of in vitro findings to human settings should be approached with caution (Fong and Wood, 2006). Sari et al. investigated the healing effect of silver nanoparticles synthesized with Nepeta cataria plant extract and integrated into pure petroleum jelly on an in vivo wound model in rats, observing a 94% wound closure after 10 days (Sari et al., 2024).

DISCUSSION AND CONCLUSION

When penicillin and other antibiotics were discovered, silver and other non-antibiotic treatments were abandoned; however, today, silver has gained significant attention due to the emergence of antibiotic-resistant strains and its low tendency to induce resistance. Due to its intrinsic therapeutic properties and multifaceted effects, silver nanoparticles exhibit broad-spectrum antibacterial capabilities against numerous microorganisms and show great potential in various applications. Specifically, they hold substantial promise in addressing emerging issues of microbial resistance, particularly in therapeutically enhanced healthcare settings (Paladini et al., 2019). In wound healing, AgNPs serve as effective antibacterial agents, preventing wound infections that can hinder the healing process and lead to chronic wounds (Astaneh et al., 2024). Silver nanoparticle-based dressings can be applied as an urgent therapy for wound healing. Current studies emphasize their ability to accelerate the healing process without causing further injury due to their capacity to protect wounds from pathogens and allow easy dressing removal (Thanh et al., 2018). Due to their broad antibacterial and antiviral spectra, there are particularly high expectations for the suppression of multidrug-resistant bacteria (Nakamura et al., 2019). Currently, AgNPs have the potential to act as an alternative to existing antibiotics, especially in response to increasing bacterial resistance (Kaabipour and Hemmati, 2021).

Nanotechnology is on the verge of revolutionizing the medical and pharmaceutical fields by providing a range of new materials and approaches. Many areas of medical care are already benefiting from the advantages offered by nanotechnology. Recently, silver nanoparticles have garnered interest for clinical applications due to their potential biological properties, such as antibacterial activity, anti-inflammatory effects, and wound-healing efficacy; these properties may be utilized to develop improved dressings for wounds and ulcers. The applications and properties of silver nanoparticles have been the focus of numerous studies. The abundance of research highlights the broad range of applications and consistently demonstrates the high efficacy of silver nanoparticles. With future studies, silver nanoparticles could be used as a primary agent in wound healing and may even contribute to a reduction in antibiotic use.

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