Antimicrobial Activity of Silver Nanoparticles against *Pseudomonas aeruginosa* in Urinary Tract Infection

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Abstract

Urinary tract infection (UTIs) is a common health concern in both community and hospital settings, affecting men and women equally. *Pseudomonas aeruginosa* is an opportunistic bacterium that causes significant acute and chronic diseases in individuals with compromised immune systems. *P. aeruginosa* has considerable intrinsic antibiotic resistance, limiting the options for successful therapies. As a result, alternative antimicrobial agents such including nanoparticles (AgNPs) are seen as promising candidates for infection management and prevention. AgNPs can deal with bacteria in various applications and are resistant to traditional antibiotics, including multiresistant strains such as *P. aeruginosa*. The dimensions of AgNPs are important in evaluating the medicinal value of nanopathy, as small particles provide more and more surface area for interaction with microorganisms, so they affect their important functions. Silver nanoparticles (AgNPs) follow microorganisms' cytoplasm and cell wall membrane, resulting in dissolution, cellular infiltration, cellular components, interaction with biomolecules, and production of reactive oxygen species and related free radicals. This chapter perfectly examines the role of antibacterial effectiveness of silver nanoparticles. Furthermore, elucidate the significance of silver nanomedicines in the treatment of urinary tract infections caused by *E. coli*.

Keywords: Urinary tract infection, *Pseudomonas aeruginosa*, Silver nanoparticles, Multidrug-resistant, Cytoplasmic membrane

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Introduction

Despite being common in both men and women, urinary tract infections (UTIs) are far more common in women because of their physiology. UTIs impact both the upper and lower urinary tracts. The infection is referred to as pyelonephritis (kidney infection) or cystitis (bladder infection), contingent upon the affected region (Neugent et al. 2020). Among the risk factors for UTIs include inadequate hygiene, sexual activity, and utilization of specific devices such as catheters, pregnancy, bladder or kidney disorders, compromised immune system, and menopause (Mansfield et al. 2022). Utilization of specific pharmaceuticals, including diuretics, and prolonged retention of urine (Pandey et al. 2022). The infection seems innocuous initially, the patient displays a range of symptoms as it advances, and in extreme instances, it may prove fatal (Suárez Fernández et al. 2021). The previously listed parameters are not exhaustive: the extent of damage, the frequency of recurrence, the manifested local symptoms, the presence of complicating disorders, and the likelihood of recurrence also differ. Kidney infections usually occur subsequent to bladder infections, potentially leading to systemic infections and, in severe instances, resulting in death. Pyelonephritis, an upper urinary tract infection, occurs subsequent to cystitis, which results from bacterial invasion of the lower urinary system, primarily involving the bladder (Wagenlehner et al. 2020), this may be attributable to a blood-borne infection (Chowdhury et al. 2024).

The urethra facilitates bacterial entry into the bladder, and both blood and lymph may also become contaminated (Figure 1). Certain strains develop Multi resistance to currently utilized antibiotics, especially carbapenems, due to adaptation and exposure to other medicines (Adekanmbi et al. 2022), they also adjust to the production of biofilms. Consequently, given the challenging nature of biofilm treatment, it is

imperative to devise novel therapeutic techniques that may effectively address both bacterial infections and biofilm formation. Therefore, using nanometric-scale materials to deliver biomolecules and antibiotics is a feasible strategy because it offers benefits like longer half-lives and systemic circulation durations, improved compound-pathogen interaction, increased absorption, and improved bioavailability, all of which lead to better therapeutic adherence and greater efficacy.

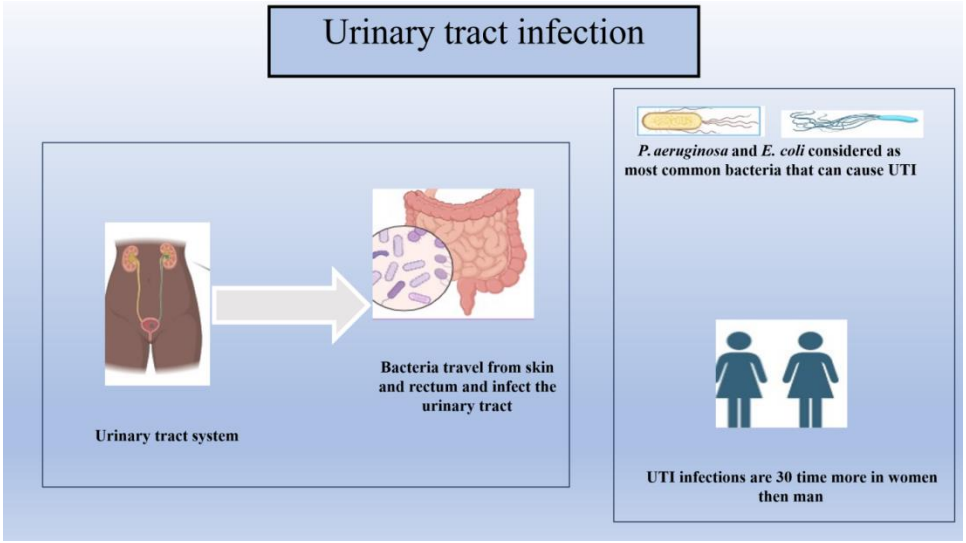

Figure 1: Urinary tract infection. Bacteria travel from skin or rectum and urethra.

UTI Epidemiology and Etiology

Urinary tract infections (UTIs) are projected to reach 93,300 cases year, constituting about 13% of all healthcare-associated illnesses. Catheter-associated urinary tract infections, the most prevalent nosocomial infection, are responsible for around one million hospital visits. With a mortality incidence of 2.3% (Wambui, 2021), the Centers for Disease Control and Prevention (CDC) notes that UTIs cause 13,000 annual deaths. Should urinary tract infections be linked to bacteremia, the rate might rise to 10%. While urinary tract infections account for 35% of recorded nosocomial infections (Chen et al., 2012). Both age and catheterization duration influences the incidence of urinary tract infections. Fifty percent of hospitalized patients with urinary tract infections are anticipated to return within 60 days (Kranz et al., 2020). Among bacterial diseases affecting newborns and children, urinary tract infections are the most common. Previous research indicates that 50% of women will at least once in their lifetime have a urinary tract infection (UTIs; 10% to 20% will contract annually, 1% to 2% will suffer from frequent bouts; 50% of women with asymptomatic bacteriuria will develop pyelonephritis (Fenta et al., 2020). Among the significant morbidities and long-lasting effects linked to pediatric urinary tract infections are chronic renal failure (Morgan et al. 2024). Increased incidence of urinary tract infections (UTIs) in patients with diabetes due to hyperglycemic urine promoting bacterial growth and colonization; these infections are prevalent during pregnancy, where cystitis can quickly progress to pyelonephritis (Kaur et al., 2022). Data from the Department of Health's Hospital Episode Statistics show that cystitis, or 0.096% of all hospital visits, accounted for 97% of hospital admissions in England over 2002–03 (Darwitz et al., 2024). The total amount of resources utilized or lost by people, businesses, and society as a whole as a consequence of an infection is the economic cost of a condition. It encompasses direct costs (such as diagnosis and treatment), indirect costs (including missed wages for patients, reduced productivity for the organization, and death costs), and intangible costs (such as expenditures associated with pain or suffering). Finding the precise economic burden could prove challenging. Five main groups define the general expenses of health care: physician appointments, hospital admissions, outpatient treatments, emergency room visits, and antibiotics linked with infections. Projected total spending for UTIs in 2000 was $2.14 billion; by 2013, it had climbed to almost $2.9 billion (Turner et al., 2015).

1. General Characteristics of *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a ubiquitous bacteria found in both terrestrial and marine ecosystems. *P. aeruginosa* is regarded as a notable medicinal bacterium owing to its remarkable adaptability to diverse conditions and its potential to cause persistent infections in susceptible persons. *P. aeruginosa* is a gram-negative, bacillus-shaped bacterium, ranging from 0.5 to 3.0 µm in size, demonstrating aerobic metabolism and featuring a single flagellum for locomotion (Nassri et al. 2021). In aerobic conditions, this non-fermentative bacterium metabolizes glucose by glycolysis, employing oxygen as the final electron acceptor. Nitrogen can function as an electron acceptor in anaerobic environments. Additionally, ATP acquisition is facilitated by the function of several membrane ATPase that regenerate ADP and H+ from prior activities (Grace et al. 2022). *P. aeruginosa* is the third most common pathogen linked to catheter-associated urinary tract infections acquired in healthcare settings *P. aeruginosa's* metabolic plasticity and environmental adaptation enable its presence in several habitats, including the human body, soil, water, healthcare facilities, sewers, and other aquatic environments such as swimming pools (Sanz-García et al. 2021).

2. Antibiotic Resistance

Antibiotics have shown therapeutic effectiveness in treating infectious diseases; nevertheless, researchers contend that this advancement

has resulted in resistance. The many forms of resistance presently observed are acquired for multiple causes. The capacity of bacteria to adapt via spontaneous or induced mutations is a major role in the development of antibiotic resistance. (Uddin et al. 2021). Bacteria acquire resistance genes by transmissible plasmids or horizontal gene transfer. Recent investigations have led to developing novel techniques for treating multidrug-resistant microorganisms. Enzyme LASB facilitates many pathophysiological processes in bacterial-host interactions, suggesting that these complex antibiotic-resistant *P.* can serve as a viable therapeutic approach to *P. eruginosa.* These metal-based antibacterial complexes attack bacteria's membranes, DNA, and RNA to interfere with vital survival processes of bacteria. In addition to these contemporary counterparts, phase and bacteriosin have been examined as antibiotic options.

2.1 Intrinsic Antibiotic Resistance

Inttrinsic antibiotic resistance is the congenital capacity of an antibiotic to be less effective because of structural or functional mechanisms that shield dangerous compounds and antimicrobial agents. *P. aeruginosa* has limited permeability, unlike certain other gram-negative bacteria. As a selective barrier to stop the passage are the asymmetric barriers of gram-negative membranes and asymmetrical antibiotics. *P. eruginosa*, nutrients have to be let in. Porin is a water permeability channel designed from barrels, allowing this access (Qin et al, 2022). *P. aeruginosa* uses a congenital process whereby its outer membrane's permeability is lowered to prevent the hydrophilic drugs from entering. It is produced by replacing selective channels that support, especially in absorbing essential nutrients, non-specific porin proteins, which they aid (Saxena et al., 2023). Clinically identified carbapenem-resistant *P. aeruginosa* points to efflux pumps as one leading cause of natural antibiotic resistance. These efflux pumps can eject antibiotics from other structurally unrelated classes or specialize in particular substrates. Resistance-nodulation-division (RND), major facilitator, small multidrug resistance, ATP-binding cassette, and multidrug and toxic chemical extrusion define the five superfamilies of efflux pumps (Kavanaugh et al., 2024). Exporting the quinolone signaling molecule PQS reveals that by reducing its concentration, the MexEF-OprN and MexGHI-OpmD systems can modulate quorum sensing (QS), therefore reducing the synthesis of virulence factors supporting ongoing infections. After being extracted from the phospholipid bilayer in the cytoplasm or the inner membrane of the bacterial cell envelope by the inner membrane protein, the outer membrane protein in this complex transports the substrates into the extracellular media.

These proteins interact with a periplasmic protein. Carried on by the AmpC gene, another natural resistance component in *P. aeruginosa* is the hydrolytic enzyme β-lactamases. Based on their amino acid sequences A, B, C, and D four types can be separated among β-lactamases. Class B β-lactamases hydrolyse β-lactams with divalent zinc ions. Classes A, C, and D hydrolyse β-lactams (Barceló et al., 2022) by an active site serine. Through outer membrane porins, a β-lactam antibiotic enters the periplasmic space and attaches itself to certain penicillin-binding proteins (PBPs). The increasing pools of 1.6-anhydromuropeptides (Klebba et al., 2021) make AmpD unable to control the elevated amounts of these fragments. When they attach to AmpR, anhydro-MurNAc peptides conformational switch UDP-MurNAc-pentapeptides, changing the protein structure. AmpR turns into a transcriptional activator, so periplasmic zone AmpC expression rises. AmpC functions as a β-lactamase, engaging with the antibiotic to facilitate its degradation. *P. aeruginosa* may produce extended-spectrum β-lactamases (ESBLs) by the acquisition of ESBL genes, rendering it highly resistant to most β-lactam antibiotics, including penicillins and cephalosporins. Antimicrobial peptides (AMPs) may facilitate the development of innovative antibiofilm antibiotics (Nasser et al., 2020). Research on the antibacterial effectiveness of numerous antimicrobial peptides is in progress (Assoni et al., 2020). Although its chiral orientation does not compromise its metabolic activity, HBD2 (human beta-defensin 2) dramatically reduces *P. aeruginosa* biofilm development at nanomolar concentrations. The reduction in biofilm development underscores the role of HBD2 in innate host defense during the first encounter between the host and the virus. Jelleine-1 (Grassi et al., 2020) is another AMP used to examine its antibacterial and toxicological properties. Jelleine-1 has, under investigation, shown minimal antibacterial effect against gram-negative and gram-positive bacteria. Amino acids were tried to be replaced in order to increase the challenge's efficacy. Trp and Arg added increased the jelleine-1 sequence's antibacterial activity. While more research is needed, this AMP may be able to treat bacterial infections categorized as gram-negative. Recent studies show *P. aeruginosa* can change its membrane to react to phosphate stress, increasing its resistance to drugs, including polymyxin B (Jones et al., 2021).

2.2 Acquired Resistance

Some drugs can acquire intrinsic resistance independent of past antibiotic use. Plasmids, for instance, lack genes for bacteria to thrive in normal conditions. However, they have genes that help bacteria thrive in hostile environments, including virulence, antibiotic resistance, and heavy metal tolerance. It has been shown that *P. aeruginosa* acquires plasmid-encoded carbapenemases (single metallo-β-lactamases), which can hydrolyse the majority of β-lactams, including carbapenems, whilst many other bacteria obtain resistance genes. Horizontal gene transfer is made possible via transformational, transductional, and conjugational processes. Bacteria acquire several resistance genes from their counterparts, including resistance to aminoglycosides, fluoroquinolones, and β-lactam resistance genes (Glen & Lamont, 2021). Usually, bacteria utilize this mechanism to disrupt the efficacy of antibiotics by disrupting pharmacological targets. One resistance strategy is quinolone target site modification; quinolones stop DNA gyrase and topoisomerase IV (Anyanwu et al., 2020), thereby preventing bacterial DNA replication. *P. aeruginosa* develops resistance to carbapenems via an acquired resistance mechanism in which changes in the outer membrane porin channel unique to OprD either decrease or completely eradicate resistance (depending on a mutation in the oprD gene or one of its regulatory proteins, such MexT) (Silva et al., 2020).

2.3 Adaptive Resistance

In contrast to other types of resistance, adaptive resistance is dependent on shifting conditions that activate cellular regulatory systems; once the triggers are removed, vulnerability often resurfaces. Biofilm-forming bacteria are known to be more immune system resistant than

other bacteria and more resistant to antimicrobial treatments. For instance, the *P. aeruginosa* biofilm matrix a key component of Edna can acidize the cellular environment, alter the permeability of the membrane, and produce structural alterations in lipid A of LPS. These modifications could cause different responses for various polymyxins or antibiotics like colistin (Lewenza et al, 2020).

3. Silver nanoparticles (AgNPs) and their antimicrobial properties

Silver is considered an effective treatment against microorganisms as it disrupts both cell membranes and metabolic processes. Silver-based nanosystems have been investigated both alone and in conjunction with other materials for the treatment of urinary tract infections. AgNPs are acknowledged as a prospective application inside nanosystems owing to their significant physicochemical features vital for fighting pathogens, including stability, colloidal form, and favorable chemical interactions. AgNPs are small reduced particles of silver with significant potential for biological applications. With sizes varying from 1 to 100 nm, they may have spherical, flat, triangular, tetrahedral, prismatic, cubic, octahedral, or irregular geometries. Consequently, there is a growing interest and expansion in research focused on the creation or modification of substances exhibiting antibacterial and antibiofilm properties, especially against strains of *P. aeruginosa* (Mikhailova, 2020).

3.1 Synthesis of AgNPs

AgNPs have several qualities and can be produced with several methods. The most often used techniques comprise chemical synthesis using inorganic reducing agents and organic solvents. Talance reagent, elemental hydrogen, sodium citrate, ascorbate, sodium borohydride. Converts metal ions into subsequently meticulously collected atoms by reducing them. Chemicals stored on the surfaces of the AgNPs generated by this synthesis can be hazardous and toxic, some especially so. This will make AGNPs useless and raise their toxicity to human cells to an unacceptable level. AgNPs may be physically synthesized using evaporation-concentration methods and laser ablation. AgNPs may be syntheszied via laser ablation, which involves introducing silver into a liquid media that absorbs laser pulse radiation. The liquid media, the laser-beating period, and the wavelength at which the laser kills the metal target influence the attributes and efficacy of nanoplashes (Rabbi et al., 2024). Additionally, electrochemical synthesis is growing in popularity, where a stable substance and silver plate electrodes are used in an electrical device with electrolytic cells (Wirtanen et al, 2021) produces a low intermediate metal salt in the cathode. Biosynthesis, which enhances stability and eliminates the need for harmful reagents and organic solvents, is the most inexpensive and ecologically benign means of producing AgNPs (Jayaprakash & Kannappan, 2022). Within nanotechnology, biosynthesis is a pertinent method and a less detrimental approach. Exogenous stabilizers help them to be created both enzymatically and non-enzymatically, at room temperature and under pressure. The reducing and stabilizing agents applied in this synthesis come from proteins, sugars, plants, algae, bacteria, yeasts, and fungi. Plants are believed to be faster than other techniques, dependable, non-toxic, and ecologically benign (Alharbi et al., 2022).

4. Antimicrobial mechanism of action of AgNPs

The prevalence of bacterial infections caused by multidrug-resistant organisms has increased dramatically over the last 20 years, primarily as a result of the careless use of antibiotics in both clinical and agricultural contexts. Therefore, there is a need to develop new treatments that target MDR strains, and AgNPs have gained more recognition in this regard. AgNPs' antibacterial activity stems from their large surface area, which promotes more interaction with microbes and kills them even at low concentrations (Tripathi and Goshisht et al., 2022). AgNPs' antimicrobial effectiveness is attributed to four distinct mechanisms: (1) adhesion to the membrane surface and cell wall; (2) AgNPs infiltration into the cell, which damages intracellular structures (mitochondria, vacuoles, and ribosomes); (3) AgNPs-induced cellular toxicity and oxidative stress due to the generation of free radicals and reactive oxygen species (ROS); and (4) modulation of the signal transduction pathway.

4.1 Adhesion of AgNPs onto the Surface of Cell Wall and Membrane

When bacterial cells are exposed to silver nanoparticles (AgNPs), the particles initially adhere to the microbial cell wall and membrane. This adhesion is primarily facilitated by the positive surface charge of AgNPs (Pokhrel et al., 2022). Due to their negatively charged membranes, microbial cells are electrostatically attracted to the positively charged nanoparticles, which enhances their attachment. This interaction leads to observable morphological alterations, such as membrane detachment from the cell wall and shrinkage of the cytoplasm, ultimately resulting in rupture of the cell wall. In addition to electrostatic interactions, AgNPs engage with sulfur-containing proteins embedded in the cell wall, causing irreversible structural damage and degradation of the wall. These disruptions compromise membrane permeability and disturb the organization of the lipid bilayer. Altered cell morphology disrupts transport mechanisms by increasing membrane permeability. The proper translocation of precursor proteins to the membrane depends on energy supplied by ATP and proton motive force (Almatroudi, 2024). The peptidoglycan in Gram-positive bacteria is about 30 nm thick and negatively charged, while in Gram-negative bacteria, it is much thinner, around 3–4 nm. The greater thickness and dense structure of the Gram-positive cell wall act as a barrier, retaining silver ions and limiting their intracellular effects (Vaiwala, et al., 2022). For instance, *Staphylococcus aureus*, a Gram-positive bacterium, exhibits greater resistance to AgNPs due to its thick peptidoglycan-rich wall, which hinders silver ion penetration.

In contrast, the outer membrane of Gram-negative bacteria contains lipopolysaccharide (LPS), which provides structural reinforcement but also contributes to increased susceptibility to AgNPs. The negatively charged LPS enhances AgNP binding to the cell surface, facilitating nanoparticle accumulation (Yahya et al., 2023). Barani et al. (2021) observed that this interaction leads to more efficient deposition of AgNPs on Gram-negative bacterial surfaces. Therefore, the relationship between AgNP concentration and treatment efficacy may vary significantly depending on the microbial class, negating a uniform dose-response correlation.

4.2 Penetration of AgNPs into Cells and Destabilization of Intracellular Structures and Biomolecules

When AgNPs engage with microbial cell membranes, they induce several forms of cellular malfunction. AgNPs are initially linked to the

cell membrane, altering its permeability, structure, and transport capacity. Conversely, once AgNPs pass the cell membrane, they can infiltrate the cells and disrupt vital biological processes (Tripathi & Goshisht, 2022). AgNPs can interact with biomolecules like proteins, lipids, and DNA as they enter microbial cells, interacting with biological structures and biomolecules that damage bacteria. (Wypij, et al., 2021). Interactions between Ag+ ions and their functional groups can deactivate proteins (Yang et al., 2024). The proteins help to generate transmembrane ATP and regulate the ion flow across the cell membrane (Girma, 2023). Breaking the hydrogen bonds between the anti-parallel DNA strands causes the Ag (+) ion to intercalate between purine and pyrimidine base pairs, weakening the double helical structure (Jiménez-Pérez et al., 2024). AgNPs induce the DNA molecule to move from a relaxed to a compacted form, reducing its replicating capacity, claims by (Vadakkan et al. 2024).

4.3 AgNPs Induced Cellular Toxicity and Oxidative Stress

Heavy metal ions like Ag^+ have a negative impact on microbial systems, as seen by increased oxidative stress. As a result, cells often benefit from a larger concentration of Ag^+ ions when it comes to reducing oxidative stress (Khan et al., 2019). Silver nanoparticles (AgNPs) show great antimicrobial potential antibacterial, antifungal, and antiviral. AgNPs' productionof ROS and free radicals, which increase cellular oxidative stress helps to explain their efficacy against bacteria, mostly (Mammari et al., 2022). Upon adhering to the cell membrane, ag^+ ions are supposed to disturb microbial signaling pathways and hamper mitochondrial respiration (Morozova, 2021). These ions disrupt respiratory chain enzymes, breaking the electron transport chain and disconnecting oxidative phosphorylation from ATP generation (Garcés et al., 2021). The concentration of free radicals that is too high destroys mitochondrial membranes, starting necrosis and later cell death. Additionally, oxidative stress causes hyperoxidation of lipids, proteins, and nucleic acids (Dyall et al., 2022). By transforming reduced glutathione (GSH) into its oxidized form, glutathione disulfide (GSSG), therefore upsetting the redox homeostasis of the cell, AgNPs also induce oxidative imbalance and death (Jiang et al., 2021). Further compromising the function of antioxidant enzymes like catalase, superoxide dismutase, glutathione peroxidase, and NADPH-dependent flavoenzymes is this imbalance (Ucar et al., 2024).

4.4 Modulation of Signal Transduction Pathways

Phosphorylating many protein substrates is known to be bacterial (Sultan et al., 2021). A signal transduction system for cellular activity and microbial proliferation in microorganisms involves the phosphorylation and dephosphorylation cycle. This method helps one understand the transduction path under the influence of the AgNP bacterial signal. Essential for metabolism, bacterial cell cycles, DNA replication, and recombination are the phosphorylated proteins generated. Furthermore, the synthesis and transport of exopolysaccharides and capsular polysaccharides are connected to the tyrosine phosphorylation of proteins in several Gram-positive and Gram-negative bacteria. AgNPs influence cellular communication and slow microbial growth by dephosphorylating tyrosine residues on important bacterial peptide substrates (Zohra et al., 2021).

5. Antibacterial activity of AgNPs against *Pseudomonas aeruginosa*

Silver has been employed for therapeutic purposes since ancient times, long before the advent of modern antibiotics. It was notably applied in treating burn injuries and open wounds due to its antimicrobial capabilities (Shrestha et al., 2024). Both Gram-positive and Gram-negative bacteria are sensitive to the antibacterial action of silver nanoparticles (AgNPs), however research indicates that Gram-negative bacteria are often more vulnerable. This increased sensitivity is explained by the distinct structure of Gram-negative bacteria, which consists of a relatively thin peptidoglycan layer and an outer membrane rich in lipopolysaccharides. AgNPs are capable of penetrating and exerting antimicrobial effects on both bacterial types (Zhou et al., 2024). Ghosh et al. (2022) state that bacterial poisoning depends on the makeup of the cell wall. With structural and physical differences, due to the protective mechanisms that allow them to come in contact with high concentrations of AGNP, toxicity for more complex species, including human cells, may vary (Tortella et al., 2020). Additionally, AgNPs consists of a positive charge compared to the negative charge of the bacterial cell membrane, which causes them to accumulate inside the membrane, causing structural changes and more permeability (Muddassir et al., 2022). The activity of AgNPs is directly affected by their dimensions, such as bacteria in small AgNPs, especially *P. aeruginosa* (Agreles et al., 2020).

6. Conclusions and Future Perspectives

The widespread misuse of antibiotics globally has contributed to the development of pathogenic microorganisms that are resistant to multiple drugs. Hospital-acquired infections represent a major public health concern because they are often difficult to treat. In this context, nanotechnology has emerged as a promising approach in combating bacteria that have developed multidrug resistance. Among the various nanomaterials, metal-based nanoparticles show potential for treating infections caused by these resistant strains. Interestingly, silver nanoparticles (AgNPs) have been used to good efficacy against pathogens including Enterobacteriaceae, multidrug-resistant *S. aureus*, and *A. baumannii* and *P. aeruginosa*. AgNPs work via a multi-level interaction mechanism. The discharge of intracellular contents brought on by the change in plasma membrane permeability causes cell death. They inhibit the synthesis of ribosomal subunits, stop DNA replication, and deactivate proteins and enzymes. AgNP toxicity depends on a number of factors, including dose, size, shape, and the presence of coating or capping agents. Compared to nanoparticles with larger diameters, those with dimensions between 5 and 30 nm are more effective against bacteria. Future studies must include the examination of possible bacterial mechanisms of resistance to nanoparticles.

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