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REVIEW

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Noble metal nanoparticles as novel antimicrobial agents: a possible solution to drug resistance

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ABSTRACT

The sudden and rapid spread of infectious pathogens, along with the emergence of multi-drug resistance, has led to an urgent requirement for the discovery of novel antimicrobial agents. In this regard, metal nanomaterials, specifically silver (Ag) and gold (Au) nanoparticles, reportedly possess significant antimicrobial activity and have the potential to be developed for in vivo and surface applications. Ag and Au nanoparticles are promising candidates for combating drug-resistant microorganisms due to their intrinsic properties. Ag nanoparticles (AgNPs), in particular, exhibit potent antimicrobial effects by disrupting cellular structures and functions, impeding microbial growth and replication. Au nanoparticles (AuNPs), although less studied, have shown potential in inhibiting bacterial growth and biofilm formation. Their versatile synthesis and surface modification methods contribute to their adaptability for different applications. This article presents a concise report on the recent progress in the synthesis, characterization, and antimicrobial properties of Ag and Au nanoparticles and the challenges involved in it.

KEYWORDS

Nanoparticles; Pathogens; Drug resistance; Antimicrobial activity; Gold; Silver

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Introduction

Infectious diseases caused by pathogenic agents such as bacteria, viruses, and fungi pose a significant global threat, affecting millions of individuals worldwide each year [1]. The rapid transmission of these diseases highlights the urgent requirement for effective treatments and preventative measures. The COVID-19 pandemic serves as a recent and notable example of how a viral infection can impact global human health and well-being in the absence of a potent treatment strategy [2]. Traditionally, a range of physical and chemical methods are utilized to inactivate the pathogens [3]. Additionally, antimicrobial and antiviral drugs are also used to inhibit microbial growth by disrupting their replication and propagation. However, these conventional approaches are ineffective in eradicating multidrug-resistant microorganisms [4].

Recently, inorganic colloidal nanomaterials have emerged as a promising solution to combat drug-resistant pathogens [5]. Plasmonic metal nanoparticles, such as Ag and Au nanoparticles, offer an alternative approach by inhibiting pathogen growth through various mechanisms. These nanoparticles possess exceptional optical and photothermal properties, stability, and tunability. They show significant potential in various areas, including in-vivo treatments and the development of antimicrobial coatings for medical devices and fabrics. This review article aims to provide a comprehensive overview of the current progress in the development of Ag and Au nanoparticles for antimicrobial application, thereby mitigating antimicrobial drug resistance.

Gold nanoparticles in antimicrobial applications

Gold nanoparticles (AuNPs) are nanoscale particles composed of gold atoms. They exhibit unique properties due to their small size, such as a distinctive optical response characterized by surface plasmon resonance. These nanoparticles are synthesized through various methods, including chemical reduction and colloidal growth. In biomedicine, AuNPs serve as effective drug delivery carriers and imaging agents, owing to their biocompatibility and tunable surface chemistry. Additionally, their catalytic properties are well utilized for various chemical reactions. The distinct size-dependent optical properties of AuNPs also enable their applications in sensing and detection [6].

AuNPs possess antimicrobial properties that depend on several factors, such as their size, shape, and surface chemistry [7]. Spherical AuNPs have been thoroughly investigated for their antimicrobial traits against a spectrum of pathogens. These nanoparticles stimulate the generation of reactive oxygen species (ROS) upon the adsorption of photosensitizers onto their surfaces [8]. The production of ROS depends on plasmonic absorption, which can be elevated and regulated by the anisotropic shapes of the nanoparticles. For instance, anisotropic gold nanorods (AuNRs) integrated into a polyurethane framework together with a photosensitizer dye have exhibited remarkable efficiency as light-triggered antimicrobial agents [9]. Various nanoparticle structures such as AuNRs and Au nanostars (AuNSs) exhibit distinct inhibitory effects against both Gram-negative and Gram-positive bacteria [10]. The advantages of anisotropic plasmon resonance extend beyond ROS generation. The facets, edges, and vertices on the surface of AuNPs serve as binding sites for various ligands, which can amplify their antimicrobial potential [7]. Concave cubic AuNPs functionalized with natural antioxidant molecules have demonstrated exceptional antibacterial action by catalyzing fatty acid oxidation and the formation of membrane pores [11]. Ultrasmall gold nanoclusters (AuNCs) with sizes less

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than 2 nm also exhibit antimicrobial properties. Their minuscule size facilitates their internalization into pathogen compartments, resulting in metabolic imbalance, ROS production, and irreversible cell damage [12].

Silver nanoparticles in antimicrobial applications

Silver inherently possesses antimicrobial properties due to its ability to release silver ions (Ag^+) upon contact with moisture [13]. These ions disrupt bacterial and fungal cell membranes, inhibiting cellular respiration and DNA replication, ultimately leading to microorganism death. This effectiveness extends to a wide range of pathogens, including antibiotic-resistant strains. This makes silver an attractive option for medical devices, wound dressings, and water purification. While its precise mechanisms are still unclear, the antimicrobial activity of silver is well-established. Silver nanoparticles (AgNPs) further enhance their antimicrobial efficacy by increasing the surface area for ion release [14]. AgNPs can also interact with microbial cells through electrostatic interactions, leading to the denaturation of membrane proteins and alterations in the exchange of biological species with the external environment. However, high concentrations of AgNPs may lead to excessive Ag^+ release and unwanted side effects to the host [15]. To mitigate such side effects and reduce the minimum bactericidal concentration (MBC) of AgNPs, functionalization of the AgNPs with targeting agents such as antimicrobial peptides (AMPs) or polycations has proven effective [16]. AMPs act on microbial membranes without entering the cells, and their combined effect with AgNPs enables the use of lower AgNP doses, enhancing biosafety. Combining commercial AgNPs with various antimicrobial agents has shown synergistic effects against Gram-negative bacteria while minimizing toxicity to mammalian cells. Efforts have also been directed towards enhancing the targeting capabilities of these functionalized AgNPs. Stimuli-responsive AgNPs, such as silver nanoclusters (AgNCs) stabilized by pH-triggered functional polymers, address concerns related to negatively charged interfaces in biological fluids. These AgNCs release Ag^+ in the acidic microenvironment of bacterial membranes, intensifying their antimicrobial effects [5].

Mechanisms of Antimicrobial Action

Mechanism of AuNPs

The antimicrobial properties of AuNPs are primarily attributed to their small size, high surface area, and photothermal properties. They disrupt the ionic interactions within the cell membrane, causing damage by interfering with pathogenic organisms [17]. Additionally, AuNPs can induce the death of bacteria and fungi by upregulating genes associated with the redox process [18]. However, the precise mechanism behind the antimicrobial activity of AuNPs remains unclear. Some studies propose that it involves targeting sulfur or phosphorus within the cell. AuNPs may bind to thiol groups in enzymes, disrupting the respiratory chain and generating an abundance of free radicals, leading to cell death [18]. They can also reduce ATP production by inhibiting the interaction between tRNA and ribosomes [19]. Another mechanism suggests that AuNPs hinder transmembrane hydrogen efflux [20]. When the AuNPs are significantly smaller than the bacterial cell, even a lower concentration can hinder bacterial growth, resulting in cell death. The nanoparticles can attach to the cell wall of the pathogen, slowing cellular processes and ultimately causing cell death. They can attract bacterial DNA through electrostatic forces on the cell wall, and their larger surface area and nano-size enhance the likelihood of cell death. Furthermore, AuNPs exhibit varied antimicrobial effects on Gram-positive and Gram-negative bacteria [21]. The contrasting characteristics of the peptidoglycan contribute to their differing responses to AuNPs. Gram-positive bacteria possess a robust peptidoglycan layer that can withstand AuNP penetration through the cell wall, whereas the thin peptidoglycan layer in Gram-negative bacteria makes them susceptible to cell death when exposed to AuNPs. Furthermore, AuNPs produced from plant extracts demonstrate higher inhibitory capabilities in contrast to those generated through chemical means [22]. The increased antimicrobial efficacy of AuNPs synthesized via green methods can be ascribed to the synergistic interaction between AuNPs and the plant extract.

Mechanism of AgNPs

While Ag atoms themselves have antimicrobial properties, the activity of AgNPs is further influenced by several key factors, including size, pH, ionic strength of the medium, and the type of capping agent on the nanoparticles' surface (Figure 1) [23]. The positively charged Ag^+ ions released by AgNPs are essential for exhibiting antimicrobial or toxic activities and must remain in their ionized state to maintain these effects. Ag^+ ions can form complexes with nucleic acids, particularly interacting with nucleosides within DNA. This interaction affects various aspects of DNA, including replication and cell propagation [24]. Additionally, Ag^+ ions can interfere with protein synthesis by denaturing cytoplasmic ribosomal components. Furthermore, AgNPs themselves can have antibacterial effects by disrupting cell membranes. Due to their nanoscale size, AgNPs can penetrate bacterial cell walls and modify membrane structures, potentially causing cell lysis and organelle disruption [25]. AgNPs may also impact microbial signal transduction pathways by affecting protein phosphorylation, leading to cell apoptosis and inhibition of cell propagation. The dissolution profile of AgNPs in the reaction medium significantly influences their antibacterial efficacy [26]. Smaller AgNPs with a spherical or quasi-spherical shape release Ag^+ ions more readily due to their larger surface area. Aggregation of AgNPs can reduce Ag^+ ion release, but this issue can be mitigated by using capping agents that modify the surfaces of AgNPs [27]. The surrounding medium can also impact Ag^+ ion release, with the presence of organic or inorganic constituents affecting AgNP dissolution by forming complexes with Ag^+ ions [28]. AgNPs release Ag^+ ions more rapidly in acidic environments compared to neutral ones [29]. The antibacterial effects of AgNPs vary, with Gram-negative bacteria proving to be more susceptible than Gram-positive bacteria [30]. Several other factors, including the surface charge of AgNPs, dosage, and diffusion state, also exert influence over their antibacterial properties. AgNPs smaller than 10 nm can directly affect cell permeability and lead to cell lysis [31]. Biofilm formation can shield bacteria from the impacts of Ag^+ ions and AgNPs [32]. Ag^+ ions may also interact with biological macromolecules, such as enzymes and DNA, through mechanisms involving electron transfer or the generation of free radicals [33]. AgNPs have been observed to hinder protein synthesis and cell wall formation, resulting in the accumulation of envelope protein precursors and disruptions in the outer cellular membrane, ultimately leading to ATP leakage.

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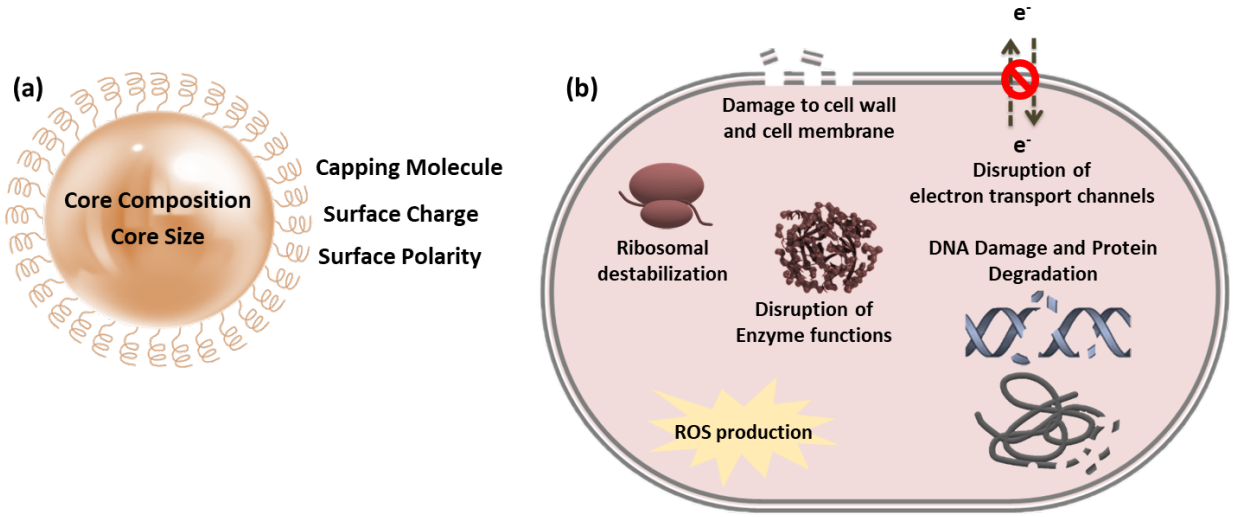

Figure 1. (a) Nanoparticle properties that affect antimicrobial activity, (b) Mechanisms of nanoparticle-induced antimicrobial activity.

Green Synthesis Methods for Producing Antimicrobial Ag and Au Nanoparticles

Metal nanoparticles possessing antimicrobial properties can be synthesized through various methods. However, the bottom-up approach, also referred to as the self-assembly approach, is mostly used for controlled synthesis. It forms nanoparticles by assembling smaller molecules or atoms into larger structures, typically with dimensions below 100 nm. The nanoparticles produced in this method are more uniform in chemical composition and have reduced surface irregularities. Among the different bottom-up approaches, the green synthesis method has gained significant attention in recent times owing to its safety, environmental friendliness, sustainability, efficiency, and cost-effectiveness when compared to traditional chemical and physical methods [34]. In green synthesis, biological components, such as phytochemicals in plant extracts and intracellular enzymes found in organisms, serve the dual roles of reducing and capping agents, converting precursor metal salt ions into nanoparticles [35]. Many phytochemicals and organic extracts inherently possess antimicrobial properties, thereby conferring similar properties to the resulting nanoparticles [36].

Various parts of plants, including leaves, flowers, fruits, bark, stems, and roots, are used for nanoparticle synthesis [37]. Plant extracts comprise diverse environmentally benign biological molecules, including enzymes, organic acids, phenols, polyols, proteins, amino acids, polysaccharides, flavonoids, and vitamins [38]. These constituents play a pivotal role in the reduction and stabilization of metal nanoparticles. The utilization of microorganisms, such as bacteria, fungi, and yeast, offers an alternative pathway for nanoparticle synthesis [39]. Bacteria can efficiently reduce precursor metal salt ions into metal nanoparticles, with actinomycetes and prokaryotic bacteria, while making the process versatile and efficient. Noteworthy bacterial species for AgNPs synthesis include *Lactobacillus casei*, *E. coli*, *Aeromonas sp.*, *Arthrobacter gangotriensis*, *Geobacter* spp., *Corynebacterium* sp., and *Shewanella oneidensis*. For AuNPs synthesis, various bacterial species like *Desulfovibrio desulfuricans*, *E. coli*, *Bacillus subtilis*, and *Shewanella* alga have been employed [40]. Fungi also play a significant role in nanoparticle synthesis. Fungi possess various intracellular enzymes that facilitate the efficient production of metal nanoparticles. Fungi have several advantages over bacteria due to the presence of enzymes, reductants, and proteins on the surface of their cells. Enzymatic reduction, either in the cell wall or within the fungal cell, has been attributed to the reduction of metal salts to nanoparticles. Yeasts, including *Saccharomyces cerevisiae*, have been reported as successful agents in the biosynthesis of both AgNPs and AuNPs [41].

Role of AgNPs and AuNPs in the Mitigation of Antimicrobial Drug Resistance

Antimicrobial resistance is the inherent or acquired ability of microorganisms, such as bacteria, viruses, and fungi, to withstand the effects of drugs or antimicrobial agents that were once effective in eradicating or inhibiting their growth. This phenomenon arises due to various genetic and evolutionary mechanisms [42]. The primary mechanisms of microbial drug resistance include mutations, which can alter the DNA, leading to changes in their target sites and reducing the effectiveness of the drug. Microbes can also acquire resistance genes through horizontal gene transfer, efflux pumps that actively remove drugs from their cells, enzymatic degradation that renders drugs inactive, and the protective nature of biofilms that can limit drug penetration. The misuse and overuse of antimicrobial agents have accelerated the development of drug-resistant microorganisms, posing a significant public health threat [43]. Inorganic colloidal nanomaterials like AgNPs and AuNPs have emerged as a promising solution for combating drug-resistant pathogens. They offer distinct advantages over traditional drugs and demonstrate particular effectiveness against antibiotic-resistant bacteria. As discussed previously in detail, AgNPs and AuNPs can interact with microbial cell membranes and intracellular components, disrupting cellular integrity. They induce oxidative stress, DNA damage, and membrane permeabilization, resulting in the inhibition of microbial growth. AgNPs possess broad-spectrum activity, which is advantageous against various resistant microorganisms. AgNPs and AuNPs, when used in combination with traditional antimicrobial agents, can enhance the effectiveness of these drugs against drug-resistant microorganisms. By targeting different cellular components and mechanisms, nanoparticles can reduce the emergence and spread of resistance.

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Challenges and Future Considerations

The use of nanoparticles in medical applications raises important regulatory concerns. Regulatory bodies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), are tasked with evaluating and approving novel therapies [44]. When considering nanoparticles, these agencies must assess their safety and efficacy thoroughly. The primary concern is the potential toxicity of nanoparticles. Nanoparticles can interact with biological systems in ways that larger particles cannot, potentially leading to adverse effects [45]. Comprehensive toxicological studies are necessary to determine the safety profile of nanoparticles. Furthermore, understanding how nanoparticles are distributed throughout the body and how they are cleared is vital. Prolonged retention of the nanoparticles in vital organs or unintended accumulation could have harmful consequences. Hence, extensive pharmacokinetic studies are required to establish safe dosage and administration routes. The long-term impact of nanoparticle exposure, particularly in patients with chronic conditions, must be examined. Chronic exposure may lead to cumulative effects that are not immediately apparent. Clinical trials and post-market surveillance are critical for assessing long-term safety.

While nanoparticles offer an innovative approach to combating microbial resistance, there is a need to investigate the potential risks associated with their use. The use of nanoparticles could inadvertently promote resistance by selective pressure. Microorganisms might adapt and develop mechanisms to counteract the antimicrobial effects of nanoparticles [46]. Research is needed to assess the likelihood and mechanisms of resistance transfer and to develop strategies to mitigate this risk. Furthermore, standardization in nanoparticle synthesis and characterization is crucial to ensure consistency and reproducibility in research and clinical applications. Standardized protocols for nanoparticle synthesis, including methods, reagents, and quality control, are necessary. Variability in synthesis can result in variations in nanoparticle properties, affecting their antimicrobial efficacy. The use of standardized characterization techniques, such as transmission electron microscopy, dynamic light scattering, and X-ray diffraction, helps in accurately assessing nanoparticle size, shape, and stability. Consistent reporting of these parameters is essential for comparing different studies and replicating results. Quality control measures, including batch-to-batch consistency and the absence of contaminants, are essential to ensure that nanoparticles used in research and clinical applications meet defined standards [47].

Conclusions

Infectious diseases stemming from pathogenic agents, including bacteria, viruses, and fungi, persist as a substantial global menace, impacting millions of individuals each year. The swift transmission of these maladies underscores the pressing demand for efficacious treatments and preventive measures. The recent COVID-19 pandemic serves as a poignant reminder of the far-reaching consequences of viral infections on global human health and well-being. Although conventional physical and chemical approaches have been employed to combat infectious agents, they frequently prove inadequate in the face of multidrug-resistant microorganisms. In recent years, inorganic colloidal nanomaterials, specifically silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs), have surfaced as a promising avenue to counter drug-resistant pathogens. They offer various advantages over organic and polymeric materials and do not contribute to the proliferation of antibiotic-resistant bacteria. While significant strides have been taken in comprehending their mechanisms of action and synthesis techniques, additional research and comprehensive assessments are imperative to address regulatory considerations, evaluate the risk of resistance development, and establish standardized procedures to ensure their secure and effective utilization in medical applications.

Disclosure statement

No potential conflict of interest was reported by the author.

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