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The Inhibitory Effect of Nanoparticles on Antibiotic-Resistant Bacteria: A Review

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Abstract
The misuse of antibiotics is a major problem that has caused genetic changes in bacteria, and increased their resistance to antibiotics, so interest has increased in using alternatives to antibiotics such as nanoparticles. The main mechanisms of resistance to various antibiotics by bacteria include horizontal gene transfer, transformation and conjugation, in addition to the mechanism of antibiotic-resistant efflux pumps that increase the ability of bacteria to adapt and survive after stress. Bacteria also resist antibiotics through the formation of biofilms and various chemical and biological pathways. Nanoparticles have been used as antimicrobials such as gold, silver and titanium dioxide nanoparticles. Nanoparticles have the ability to enhance antibiotics to reduce the minimum inhibitory concentration required to inhibit bacterial growth, making antibiotics more effective, or they act as strong antimicrobials in themselves. Our research focused on analyzing the antimicrobial mechanisms of nanoparticles on general bacteria and antibiotic-resistant bacteria and comparing the value of nanoparticles prepared by different functional techniques. Considering the potential use of antibacterial agents in medicine, the toxic effect of antibacterial agents on eukaryotic mammalian cells is of great importance, and this review summarizes the available experiments based on the cytotoxicity data of various antibacterial nanoparticles. In conclusion, since each type of nano antibacterial agents has a diverse and reliable system for its antibacterial ability, and their shape, size, or surface functional groups can be designed and modified at the molecular level, they have currently been tested for broad-spectrum antibacterial agents and against various types of bacterial applications. This flexibility means that based on the scope of the manufacturing method and its anti-infective performance, we can develop a good nano antibacterial agent that is more in line with the requirements of the pharmaceutical market development; the final application to the patient in the clinic.

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1. Introduction

The rapid global spread of antibiotic-resistant bacteria has become a massive public health threat and is considered to be a crisis for community and hospital medicine. In particular, the therapeutic measures for antibiotic-resistant bacteria are rarely effective or even life-threatening. To address this, researchers are looking for and developing new classes of alternative strategies to reduce the death rate from bacterial diseases potentially (Serwecińska, 2020, Aljeldah, 2022) [52, 5]. Although there are many new classes, such as antimicrobial peptides, phage therapy, gene therapy, bacteriophage endolysin, and other strategies that can kill multi-drug-resistant pathogens, some of them are still in the clinical trials phase, whereas others have not yielded efficacious results for therapeutic purposes. Compared to other strategies to develop new alternative treatments, one of the potential sectors is nanotechnology, especially the use of nanoparticle technology, which focuses on developing the most effective drugs ever to respond to the unique complexities of biological systems and multiple resistant pathogens (Khan *et al*.2022, Malik *et al*., 2023, Kumar *et al*., 2020) [28, 40, 30]. Nanoparticles are characterized by unique properties, making them ideal for application in a wide range of therapeutic and diagnostic medical activities. Moreover, nanoparticles have stronger antibacterial properties against antibiotic-resistant pathogens.

The following is a systematic review of the potential of the use of nanoparticles in several metal oxides or non-metal oxides, of the metal nanoparticles that have been proven to suppress emerging antibiotic-resistant bacteria and the prospect of studies on the use of nanoparticles (Gómez-Núñez *et al*. 2020, Essa *et al*.2022, Kamaruzaman *et al*. 2022) [20, 18, 26].

2. Understanding Antibiotic Resistance

Antibiotics are commonly used in many healthcare facilities, including hospitals, clinics, and animal healthcare facilities, to prevent and cure diseases. However, antibiotic-resistant bacteria are having an impact in many areas of healthcare. Infections caused by these resistant bacteria cause discomfort, increase mortality, and complicate healthcare facilities (Serwecińska, 2020, Serra-Burriel *et al*.2020) [52, 51]. Increased cases of multidrug resistance have made it difficult to treat and cure infections caused by these resistant pathogens. The inappropriate overuse of antibiotics is one of the main causes of the development of antibiotic resistance. The effect of these resistant bacteria creates a burden on both public health and economic sectors. Research is being carried out to develop new antibiotic classes or to increase the effectiveness of existing antibiotics. Research and development of new classes of antibiotics should be carried out in the global action plan for controlling antimicrobial resistance (Wong *et al*. 2021, Dache *et al*., 2021) [65, 41]. The causes and consequences of antibiotic resistance are known, but the factors that reduce the antimicrobial effect of antibiotics are also expected to be addressed. One approach to solving this problem is to use metal nanoparticles. In addition, metal nanoparticles have been shown to have significant antifungal and antiviral effects, although they also have high antibacterial and antimicrobial effects, which are considered relatively toxic and resistant (Alavi *et al*.2022, Sharmin *et al*. 2021) [4, 51].

2.1. Mechanisms of Antibiotic Resistance

Antimicrobial resistance represents one of the greatest threats of the 21st century. In the evolution of antibiotic resistance, there are many cross mutations among bacteria under natural selection. The main mechanisms of spreading antibiotic resistance include horizontal gene transfer, transformation, and conjugation (Saha & Sarkar, 2021, Aljeldah, 2022) [49, 5]. There are many resistant genotypes from the ultimate parental allele. There are numerous biochemical expression pathways or different ways at the regulatory level. The path of resistance is divided into specific and non-specific. When bacteria experience selection in the environment, non-specific resistance begins to develop first. However, no specific resistance genotypes exist, but when the environment of the population inhibits growth, the specific genotype for specific resistance significantly arises (Iskandar *et al*. 2022) [25].

Multiple efflux pumps exist in different genotypes for the affected resistant antibiotics and increase the adaptability and survival rate of bacteria after stress. In the prevention of bacterial diseases, there are many biofilm formation pathogenic factors. Genetic variation and changes in the living environment can control biofilm-forming pathogenic factors. These allow the pathogenic bacteria to form biofilm-related phenotypes in the shortest time, to block out antibiotic stress, and to improve the hindering effects of antibiotics (Roy *et al*. 2021, Grimsey *et al*. 2020) [47, 22]. This finding provides a theoretical basis for the design of adaptive control strategies for gram-negative bacteria in future scientific research. In bacteria, the expression of the target genes and protein products of the plasmid conjugation transfer function is closely related to the living environment. The evolution of argK gene-encoded factors leads to the evolution of medical microbiological experimental treatments. This discovery makes it possible to find that a low amount of inorganic nanoparticle carrier can hinder the argK gene. The formation of protein-encoded factors can prevent drug resistance from transferring effective mechanisms for inhibiting new gene solubilization mechanisms (Ebrahimi *et al*. 2023, Piperno *et al*. 2021) [17, 45].

3. Nanoparticles as Potential Solutions

Nanotechnology is an ever-growing field with an array of applications. Nanoparticles, specifically, have shown promise to bolster antimicrobial strategies. Such interest exists because of the unique properties catalytic nanoparticles generally possess, such as antimicrobial capabilities and surface area. To date, researchers and investigators have expressed interest in the antimicrobial potential and synergy a few categories of nanoparticles possess: silver, gold, and titanium dioxide (Saeed *et al*. 2023, Bhattacharjee *et al*. 2023, Karnwal *et al*.2023) [48, 47, 27]. These materials have recently been studied for their impact on the growth of antibiotic-resistant planktonic and/or biofilm bacteria. It has been shown that particles are capable of either enhancing antibiotics to decrease the minimum inhibitory concentration necessary to stop bacterial growth, essentially making the antibiotics more effective, or acting as potent antimicrobial agents themselves (Skwarczynski *et al*. 2022, León-Buitimea *et al*. 2020, Vassallo *et al*. 2020) [55, 31, 62].

By making antibiotics more effective, one can reduce the rate of bacteria becoming antibiotic-resistant while simultaneously lowering the dose of antibiotics used in a clinical setting, therefore abating the potential toxicity delivered to humans. While during low-level exposure, no cytotoxic effects are noted, long-term inhalation or consumption of these agents has the potential of conferring toxic effects to a human or animal host (Clausen *et al*. 2020, Guo *et al*. 2021, Miravitlles *et al*. 2021) [13, 23, 42]. The unique antimicrobial properties nanoparticles possess have allowed for new diagnostic tools to be developed that can aid in the rapid identification of the causative species of a bacterial infection. Such strategies include antimicrobial susceptibility testing and spectroscopy, as well as utilizing nanoparticles to target and kill bacteria in a biofilm. As the field of nanotechnology rapidly expands in the direction of solution-oriented outcomes, it is important to remain informed of other attributes such as toxicity and biocompatibility to continue the improvement in human health (Staroń and Długosz 2021, Zhang *et al*.2022) [51, 69].

3.1. Types of Nanoparticles

In recent years, due to the changes in human resistance to antimicrobial drugs, physical antibacterial agents are extremely important. Among them, the use of nanoscale drug carrier systems, nano-antibacterial drug films, and nano-antibacterial solutions shows significant antibacterial effects, demonstrating great potential and broad application prospects (Osman *et al*.2022, Zong *et al*.2022, Vassallo *et al*.2020) [43, 69, 62]. At present, nanoparticles that exhibit significant antibacterial capabilities mainly include metal-based

nanoparticles, metal oxide nanoparticles, and carbon-based nanoparticles, among which silver nanoparticles and their related functional materials are the most commonly used. In addition, other antibacterial nanoparticles also include liposome nanoparticles and hormone-based nanoparticles. This section summarizes the antibacterial activities of commonly used nanoparticles that have been subjected to substantial antibacterial activity evaluations (Ayanda *et al*.2024) [7].

Our focus is on analyzing the antimicrobial mechanisms of nanoparticles on general bacteria and antibiotic-resistant bacteria and comparing the value of nanoparticles prepared by different functionalization techniques. Considering the potential use of bacteriostatic agents in medicine, the cytotoxic effect of bacteriostatic agents on eukaryotic mammalian cells is critical, and this review also summarizes the available experiments based on the cytotoxicity data of various antibacterial nanoparticles (Tripathi & Goshisht, 2022, Makvandi *et al*.2020, Canta & Cauda, 2020) [61, 38, 11].

In conclusion, because each type of nano-antibacterial agent has a diverse and reliable system for its antibacterial ability, and their shape, size, or surface functional groups can be designed and modified at the molecular level, it has currently been tested for broad-spectrum antibacterial agents and against different types of bacterial applications. This versatility means that based on the scope of the manufacturing method and its anti-infection performance, we can develop a good nano-antibacterial agent that is more in line with the development requirements of the drug market; the final patient application in the clinic is a long-term research competition (Liu *et al*. 2020, Liu *et al*., 2020, Ahmad, 2021) [33, 34, 1].

4. Inhibitory Mechanisms of Nanoparticles on Bacteria

The possible inhibitory mechanisms of nanoparticles on bacteria can be summarized as follows: nanoparticles mainly damage the structure and function of key components of bacterial cells (including the double layer of the cell membrane, the cell wall, the genes, the enzymes, and the structural proteins), which leads to the loss of material and energy metabolism, catalyst poison, and the obstruction of bacteria in combination with antibiotics. Moreover, other inhibitory mechanisms are involved in the oxidative stress caused by the generation of reactive oxygen radicals and the changes in membrane potential, in which the former and the latter probably trigger the apoptosis of bacteria and induce reproductive dysfunction, respectively (Godoy-Gallardo *et al*. 2021, Shkodenko *et al*., 2020, Linklater *et al*. 2020, Díez-Pascual, 2020) [19, 54, 32, 16].

When nanoparticles destruct the bacterial cell membrane, ions and low-molecular substances in the bacterial cell will outflow; however, the macromolecules, such as DNA, RNA, proteins, and other cytoplasmic nutrients, will also be outflowed, communicating the disruption of bacterial metabolism, which will result in the efflux of protons and oxidative phosphorylation, thereby leading to the depression of energy (Ahmed *et al*.2020, Khorsandi *et al*. 2021, Wang *et al*. 2023) [3, 29, 63]. Then, metal ions or other cationic nanoparticles will couple with the energy-producing respiratory chain of all bacterial cells and cause uncoupling. At the same time, chemical materials generated from metal nanoparticles' function can enhance cellular metabolism disorder, increase the concentration of reactive oxygen radicals, and aggravate pathogenic conditions. For instance, imaging showed that the damage to the double layer of cells has been detected after the treatment with zinc oxide nanoparticles, as these cells release a large amount of nucleic acid matter (Canaparo *et al*., 2020, Horie & Tabei, 2021, Makhdoumi *et al*. 2020) [10, 24, 36].

4.1. Cell Membrane Disruption

Cell Membrane Disruption. The antibacterial action of nanoparticles has been closely linked to the ability to localize and penetrate bacterial cell membranes. In Gram-negative bacteria, the cell envelope consists of an outer membrane containing a lipid A layer on the external side and an underlying peptidoglycan layer covalently linked to lipoproteins. The underlying cytoplasmic peptidoglycan layer is present. In Gram-positive bacteria, the cell envelope contains only a peptidoglycan layer. (Linklater *et al*. 2020, Yin *et al*. 2020, Chandrasekaran *et al*., 2020) [32, 67, 12].

Membrane penetrations involve two related processes, including membrane destabilization and the formation of small nanoscopic channels, which tend to possess overlapping characteristics. Once very large lesions have formed, continued membrane disruption facilitates bacterial cell lysis. However, the ability of the nanoparticles to create small nanoscopic nanochannels permits cytoplasmic proton flow, selectively causing only the bacterial inner membrane to depolarize (Pagnout *et al*.2021, Malhotra *et al*.2023, Makvandi *et al*. 2023) [44, 39, 37]. This results in the termination of ATP production and ion transport, subsequently leading to cell death. Importantly, many developed bacterial resistance mechanisms against existing antibiotics may not work against the action of nanoparticles on bacterial membranes. Both the destabilization and small nanochannels were strongly influenced by the nanoparticle size, shape, surface chemistry, solution ionic strength, and charges on the bacterial cell. Thus, both small particles that only disrupted the membrane and large particles that also caused cell lysis can be used to combat bacterial infection (Amaro *et al*. 2021, Mba & Nweze, 2021, Makabenta *et al*. 2021) [6, 41, 35].

5. Applications and Future Perspectives

5.1. Wound Healing

Efficacy of the nano antimicrobial agents: Before, the gold standard of wound therapy was treatment with zinc, but today there are many successes in the use of metal compounds (Gowda *et al*.2023) [21].

5.2. Coating of Medical Devices

Nanomaterials in the existing market for medical devices: There are many companies that sell coatings containing amorphous iron, composed of micron or nano particles. A scan showed microparticles with nano clusters ranging in size from 200 to 300 nm. Some of the other fines are also used for the purpose of antimicrobial sterilization and strategies. For long-term implants, it is more thermo-tolerant and can especially be used in urinary catheters to prevent biofilm. Nanoparticles of titanium dioxide and silver were used in polysulfone and cathrami coated membranes to prevent bacterial membrane formation ex vivo. Chronic systemic medication of patients in immunocompromised or hemodialysis patients was taking systemic medications (Samree *et al*.2020, Soo *et al*., 2020) [50, 56].

5.3. Systemic Therapy

The significant decline in antibiotic effectiveness over time

has led to the development of many strategies to address gram-positive and gram-negative pathogens. Strategies like phage therapy, antimicrobial peptides, and nanomaterials have shown promise in the laboratory, and some of them are up to first tests in humans. Nanomaterials combined with heat can also be utilized in these fields. It is recommended to accelerate the transition of these potential candidates for human use. A better understanding can help to promote innovation in this field. This success and the ability to push more nanoparticles into the clinic can continue in the longer term. Requirement: There is a need for major communication, cooperation, and authorship of the findings in the area where scientists, medical experts, and laboratory authorization must be implemented as policy makers and regulators, in terms of translation of disease and disease areas, particularly in the field at risk of comprehensive infection. A collaborative strategy can increase decisions with a short lifespan in the next 3–4 years. Startup approval for human trials can be obtained within this time frame. Key opinion leaders and governance support are needed sooner rather than in 2–3 years (Barani *et al*.2021)(Tavares *et al*.2020, Ahmad *et al*., 2020) [2, 56].

6. Conclusion

Even in the current age of antibiotics, the development of antibiotic-resistant bacteria has led to appalling consequences, reinforcing the demand for innovation and the need to find alternative solutions. In this review, we have summarized a wide range of research demonstrating that the use of nanoparticles to fight multidrug-resistant bacteria can be an effective strategy for reducing, and sometimes completely eradicating, resistant strains. Nanoparticles can exhibit antimicrobial properties via various mechanisms, such as the permeabilization and disruption of the bacterial membrane, the generation of reactive oxygen species, the induction of genotoxicity through DNA damage, the interference with electron transport chains, and by affecting chromosome dynamics and ribosomal subunits. In vivo animal studies have shown promising results following intravenous and inhaled application of nanoparticles, and further research into the anticipated use of metals could reveal their practical application and pharmacological properties in clinical settings. While a dedicated review of regulations and approval processes for nanoparticle application in healthcare scenarios would undoubtedly be fruitful, current antimicrobial stewardship strategies are hindered by the emergence of new resistant strains after antibiotic use, so we anticipate that research in this field will pave the way to novel antimicrobial compounds and materials with the potential to significantly enhance public health.

With a growing number of studies indicating that antimicrobial conjugated nanoparticles have the potential to reduce the levels of multidrug-resistant bacteria not only in environmental settings but also in in vivo preclinical models, the field of materials science is in the position to develop new drug products that could effectively combat severe infections. Despite the need for a better understanding of how nanoparticles work in the human body and the potential challenges for their development and approval, we believe that these new tools might represent a viable alternative to tackle pathogens that are difficult to treat in critically ill patients.

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