Review Article

Antimicrobial Feature of Nanoparticles in the Antibiotic Resistance Era: From Mechanism to Application

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Abstract

The growth of nanoscale sciences enables us to define and design new methods and materials for a better life. Health and disease prevention are the main issues in the human lifespan. Some nanoparticles (NPs) have antimicrobial properties that make them useful in many applications. In recent years, NPs have been used as antibiotics to overcome drug resistance or as drug carriers with antimicrobial features. They can also serve as antimicrobial coatings for implants in different body areas. The antimicrobial feature of NPs is based on different mechanisms. For example, the oxidative functions of NPs can inhibit nucleic acid replication and destroy the microbial cell membrane as well as interfere with their cellular functions and biochemical cycles. On the other hand, NPs can disrupt the pathogens' lifecycle by interrupting vital points of their life, such as virus uncoating and entry into human cells. Many types of NPs have been tested by different scientists for these purposes. Silver, gold, copper, and titanium have shown the most ability to inhibit and remove pathogens inside and outside the body. In this review, the authors endeavor to comprehensively describe the antimicrobial features of NPs and their applications for different biomedical goals.

Keywords: Antibiotic, antimicrobial feature, application, mechanism, metal nanoparticles, nanoparticles

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Submitted: 26-Feb-2024; **Revised:** 20-May-2024; **Accepted:** 21-May-2024; **Published:** 30-Nov-2024

Introduction

Nanoparticles (NPs) are progressively being adopted as an alternative to antibiotics for managing bacterial infections. They have a multitude of applications, such as antimicrobial coatings on implantable devices and medical materials to prevent infection and promote wound healing, bacterial detection for diagnostic purposes, and antibiotic delivery systems. Even though the precise mechanisms behind their antimicrobial actions and real-life toxicity are not fully comprehended, current theories revolve around oxidative stress induction, metal ion release, and nonoxidative mechanisms. The necessity for multiple simultaneous gene mutations in a single bacterial cell makes it difficult for bacteria to develop antimicrobial resistance to metal NPs effortlessly.[1,2]

Some NPs are employed as antimicrobial agents, exhibiting diverse physical and chemical characteristics.[3] NPs integrate organic-based liposomes and capsules filled with conventional antibiotics or cutting-edge RNAs, called nanocarriers. Furthermore, certain NPs exploit the release of cations from metal colloid surfaces, functioning as the primary antimicrobial mechanism.[4,5] These metal colloids can be fine-tuned to incorporate various chemical elements, such as silver (Ag) or gold (Au), and surface functionalities, such as stabilizing agents or surface charges. Their primary particle

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_92_24

How to cite this article: Salmani-Zarchi H, Mousavi-Sagharchi SM, Sepahdoost N, Ranjbar-Jamalabadi M, Gross JD, Jooya H, *et al*. Antimicrobial feature of nanoparticles in the antibiotic resistance era: From mechanism to application. Adv Biomed Res 2024;13:113.

size can be engineered to be less than 15 nm in diameter, facilitating passive diffusion across bacterial cell walls and other intracellular membranes, or larger than 50 nm to prolong cation leaching in biological or environmental matrices. If the antimicrobial activity of each property is assessed, safe and effective antimicrobial NPs can be developed.[6]

The evolution of nanotechnology, specifically in NP engineering, together with accumulating knowledge about infectious diseases, has driven significant progress in antimicrobial drug delivery. Substantial efforts have been invested in designing numerous NP-based platforms, encompassing liposomes, polymeric NPs, dendrimers, and inorganic NPs [Table 1]. These methods have showcased their effectiveness in addressing bacterial pathogens by supporting targeted, responsive, and combinatorial antibiotic delivery, successful antimicrobial vaccination, and rapid bacterial detection. It is anticipated that continuous improvements in nanotechnology will result in more sophisticated antimicrobial delivery systems, thereby cultivating more effective, patient-friendly, and cost-efficient therapeutics, as well as improved detection techniques for a broad spectrum of infectious diseases.[7]

The appearance of antibiotic-resistant bacterial infections, originating from acquired resistance and/or biofilm formation, warrants the establishment of novel and innovative therapeutic strategies.[8,9] Nanomaterial-based therapies hold potential in confronting difficult-to-treat infections due to their ability to evade existing drug resistance mechanisms. Moreover, nanomaterials' unique size and physical attributes empower them to target biofilms and surmount chronic infections. Furthermore, hybrid NPs and metal nanohybrids are novel suggestions to improve the gap between antimicrobial features and NP resistance in bacteria. Here, we underscore the general mechanisms through which nanomaterials target bacteria, thereby controlling infections linked to acquired antibiotic resistance or biofilms. Furthermore, we investigate the design aspects of these nanomaterials, how their antimicrobial mechanisms contribute to augmenting their efficacy, and the types and factors involved in the success of this mission.

Antimicrobial Features and Mechanisms

Antimicrobial NPs are a promising alternative to conventional agents, such as antibiotics and antifungals, due to their unique characteristics; they can be divided into metal, metal oxide, carbon-based, polymeric, and lipid-based NPs. These NPs can kill various types of germs effectively and are highly effective even at low concentrations.[10,11] Importantly, most of them are minimally toxic to human cells and tissues, ensuring a safe profile. For example, investigations have shown that metal oxide NPs like zinc oxide (ZnO) exhibit selective antibacterial activity with minimal effects on human cells.[12,13] Antimicrobial NPs also have an extended shelf life and stability as well as the potential to overcome drug resistance, making them valuable in antimicrobial therapy.[14] AgNPs are broadly studied and used in antimicrobial applications because of their broad-spectrum activity against bacteria,[15,16] fungi,[17,18] viruses,[19,20] and parasites.[21,22] AgNPs damage microbial cells by affecting membranes, DNA, proteins, and enzymes by releasing Ag^{+} ions.[23] They also enhance antibiotic effectiveness and reduce biofilm formation.[24,25] Similarly, AuNPs exhibit antimicrobial potential through interactions with microbial cells, generating heat or reactive oxygen species (ROS) that destroy the microbes.[26,27] Additionally, AuNPs can serve as carriers for other antimicrobial agents like antibiotics or peptides.[28] Copper NPs (CuNPs) constitute another category of metal NPs exhibiting antimicrobial attributes. They discharge $Cu^{+/2+}$ ions that compromise the stability of the microbial cell membrane and metabolic processes. CuNPs can also induce oxidative stress and DNA damage within the microorganisms. Their antibacterial activity is particularly potent against both Gram-positive and Gram-negative bacteria as well as some viruses and fungi.[29,30] Titanium NPs (TiNPs) primarily consist of titanium dioxide (TiO_2), which serves as a widely employed photocatalyst.[31,32] Under ultraviolet or visible light exposure, TiO_2 can generate ROS capable of oxidizing and degrading microorganisms.[33,34] Its antibacterial effectiveness extends to bacteria[35] and additionally to certain fungi[36] and algae.[37] Practical uses of TiO_2 include self-cleaning surfaces.[38] The exact ways that NPs kill germs are not fully known, but there are several possible ways to explain them.[2]

Table 1: Types of NPs

Organic NPs	Inorganic NPs
Polymeric micelles	AgNPs
Polymersome	AuNPs
Dendrimer NPs	FeNPs
Nanolipid carrier	Calcium phosphate NPs
Liposome	Mesoporous NPs
Nanoemulsion	Quantum dots

Mechanism of antimicrobial actions

NPs are receiving attention for their remarkable ability to destroy the cellular structure of pathogens through various mechanisms. To effectively act as agents, NPs need to reach the pathogens. NPs interact with pathogens through electrostatics receptor-ligand binding, van der Waals forces, and hydrophobic/hydrophilic interactions.[39,40] Once NPs have gained access to the cell, they can enter through various types of endocytosis, such as clathrin-mediated and caveolin-mediated endocytosis, as well as phagocytosis and pinocytosis.[41,42] Metal and metal oxide NPs are able to inhibit pathogens by generating ROS [Figure 1].[43] Certain metal NPs (e.g., Ag, Cu, and Zn) can release metal ions that disrupt essential cellular metabolic functions in microbes, including DNA, protein synthesis, and enzyme activity. These metal ions can also induce oxidative stress and generate ROS, damaging vital cellular components.[29,44] Other NPs, like Au, iron oxide (Fe_2O_3), and TiO_2, can generate heat or

ROS when exposed to specific stimuli, leading to thermal or oxidative damage to microbes.[45] NPs such as carbon nanotubes, graphene oxide, metal NPs, metal oxide NPs, and chitosan can physically interact with the cell membranes of microbes, compromising their integrity and permeability. This can result in leakage of microbe cytoplasmic contents and loss of their cellular functions.[46,47] Additionally, NPs such as liposomes, polymeric micelles, and dendrimers can act as carriers for antimicrobial agents, enhancing solubility, stability, bioavailability, and specificity. They can also protect against degradation and resistance, enabling controlled release at the target site.[48,49] Therefore, NPs hold promise in combatting pathogens, with ongoing research and potential to address microbial threats and evolving challenges. Here, we will focus on metal and metal oxide NPs with antimicrobial applications: Ag, Au, Cu, and Ti. Varying mechanisms of action are described in Table 2. Microbes exhibit different infective mechanisms. Different virulence factors are presented and synthesized by pathogens to accomplish their infective survival and reproduction goals. Similarly, NPs have different mechanisms for inhibiting different pathogens such as bacteria, fungi, and viruses.

Table 2: NPs' different mechanisms of action on microbial cell structures, a quick view[50]

Type of NP	Mechanisms of action
Ag	Inhibit the DNA ability to replicate and damage cells in the G2 phase
Au	Inhibit the ability to bind the tRNA to the ribosome
CuO	By damaging the cell membrane, critical enzymes of bacteria are inhibited
TiO_2	Generate the ROS and cause oxidative stress
ZnO	Membrane dysfunction
MgO	Harms the cell membrane and causes the structures inside to leak out
Al_2O_3	Leakage of intracellular content by damage to the cell membrane

NPs express different mechanisms of action by DNA damaging for inhibiting bacterial virulence and bacterial growth, which are generally divided into two groups: oxidative and nonoxidative. Some of the NPs (e.g., Ag and Ti) are able to activate the oxygen and produce OH and RO ions. RO ions can destroy the cellular structure of bacteria by damaging the cell membrane and inhibiting bacteria proliferation.[51] Nonoxidative mechanisms contain a wide range of different cellular mechanisms. DNA damage by releasing heavy metal ions is one of the usual actions of NPs (e.g., Ag). Furthermore, heavy metal ions can destroy cellular membranes and leak the cell's contents.[52,53] By damaging the membrane of bacteria, cellular organelles and membrane properties (e.g., proton pump) will be dysfunctional.[54] As a result of these mechanisms, the function and reproduction of bacteria are inhibited.

Fungal infections in different organs of humans, in particular, the respiratory system, are dangerous and have great mortality.[55,56] The wonderful potency of NPs in the inhibition of fungi is demonstrated in different studies. For example, Panacek *et al*. demonstrated AgNPs' effect on *Candida* spp.[57] They observed that AgNP is effective on the cell wall of the yeasts by inhibiting the synthesis of vital proteins in mitochondria or by depolymerization of ribosomes.[58] AuNP is also effective on intracellular pH by inhibiting the H^+ ATPase and leads to cell death for low pH.[59] ZnO NPs are another effective NP on fungi and inhibit the permeability of the membrane by its activity.[60] ROS practically inhibit any live fungal cell from surviving. DNA-related functions of other unicellular fungi-like microorganisms are also weak against ROS.[61]

Most severe and highly contagious infections are related to viruses, with the main role in critical conditions of pandemics throughout history. In the first replication of the virus, NPs (e.g., Fe_2O_3) can inhibit the RNA transcription and budding in viruses, particularly in H1N1 influenza.[62] AgNP is also one of the most efficient ways to inhibit the viral particles that are necessary for virus penetration. It

Figure 1: Mechanisms of antimicrobial action by NPs. In general, microbes are divided into three categories: bacteria, viruses, and fungi. In this picture, the antimicrobial mechanisms of NPs are presented in cellular scale. ROSs are one of the most important components in inhibiting microorganisms

can be effective on human immunodeficiency virus (HIV)-1 by stopping the post-entry life cycle, so it can prevent and control the viral attack in cells.[63] AgNP is potent to inhibit other viruses (e.g. monkeypox, hepatitis A virus (HAV)-10, herpes simplex virus (HSV)-1, coxsackie virus type B) by the obscure mechanism.[64] AgNPs have an inhibitory role in H1N1 influenza by deactivating the viral penetration to host cells.[64] CuNPs demonstrated a good effect on the calicivirus by ROS generation in the Shionoiri *et al*. project.[65]

Effective Factors in Antimicrobial Features

The structure, composition, and properties of different NPs affect their antimicrobial activity and determine which antimicrobial mechanism they employ. As discussed earlier, metal NPs such as Ag, Au, Cu, and Fe can release metal ions that disrupt bacterial function.[66] Metal oxide NPs such as zinc oxides, titanium oxides, and copper oxides can damage bacterial cellular components by producing ROS. Some other NP types can physically interact with bacterial cells and disturb the membrane or cause mechanical damage. Besides the types of NPs that induce different mechanisms of action for antimicrobial effects, as discussed in the previous section, other factors such as shape, size, surface properties (roughness, zeta potential, and doping modification), and environmental factors (pH, temperature, salinity, and presence of organic matter) can modify the physical and chemical properties of NPs and lead to various outcomes of microbial agents [Figure 2].

Size

The antimicrobial effects of NPs can also depend on their size. The optimal size of NPs varies depending on their type, but in general, NPs with smaller sizes have more surface area compared to their volume, which implies more likely interaction with the environment or the bacterial membrane. Smaller NPs can also produce more ROS and dissolve faster as well as release more metal ions. Some types of NPs can penetrate or interact more easily with bacterial cells when their size is smaller.[67-69]

For instance, many studies showed that the microbial activity of AgNPs has an inverse relation with their size. AgNPs' antimicrobial properties increase significantly when their size is below 10 nm. AgNPs' hydrodynamic diameter below 6 nm

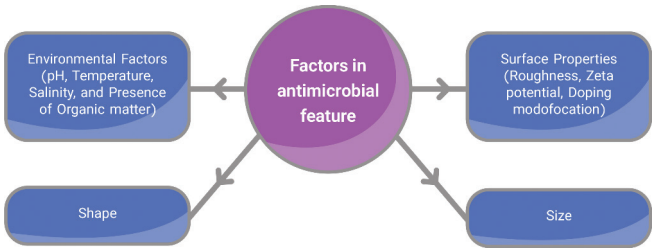


Figure 2: The antimicrobial activity of NPs is influenced by various factors, such as environmental conditions (pH, temperature, salinity, and organic matter), surface properties (roughness, zeta potential, and doping modification), and morphological characteristics (shape and size)

enables their elimination through the kidney and consequently reduces the long-term risk of damage due to prolonged exposure to silver.[70,71] These NPs can easily enter because of their small size to the bacterial wall and accumulation of ROS results in more intense destruction. Moreover, functionalized AgNPs with small or medium sizes strongly affect phagocytosis, autophagy, and mitochondrial electron transport.[70,72] Smaller selenium oxide (SeO_2) and tellurium oxide (TeO_2) NPs have higher antimicrobial activity because of higher production of ROS and a strong link between their antimicrobial activity and their dimensions.[73]

Shape

NPs' shape is effective in their antimicrobial properties. NPs can have various shapes such as spherical, rod, cube, star, cluster, cone, pyramid, disk, and flower.[74] Some articles suggest that there is no direct relation between the shape of an NP and the antimicrobial effect; however, other articles show such an effect.[75,76] Different shapes can have different surface area to volume ratios, surface energies, crystal facets, and surface charges, the properties that can influence the interaction between them and the environment or the bacteria's surface. Different shapes can also generate different types and amounts of ROS, dissolve at different rates, and release different amounts of ions.[77] Moreover, different shapes can have different physical interactions with bacterial cells. It is also suggested that the similarity between NP shape and receptor morphology of bacteria may enhance contact and interaction.[75]

S Tang and J Zheng studied the relation between the shape of the bacteria and the relation of the affection action with the shape of AgNP. They suggested that among the rod-shaped, spherical, and truncated triangular against *Escherichia coli (E. coli)*, the effectiveness and biocidal activity were the highest in truncated triangular AgNP. The next places were taken by spheres and rods, respectively. This was related to the number of truncated triangular facets which helped them to have higher surface binding and eventually higher cell uptake and cell death.[71] ZnO, an economical substitute for antimicrobial NPs such as Ag, also shows a relation between ZnO NP activity and shape. It was revealed that the ZnO in the shape of cuboidal shows higher antimicrobial activity than spherical and hexagonal structures.[75] Rajat K. Saha *et al*.[78] found that ZnO NPs with a flower shape can kill *E. coli* better than ZnO NPs with a hexagon shape that has gaps. These researchers used the methods of making ROS with light and releasing Zn^{2+} ion.

Surface properties

Some of the surface properties, such as roughness, zeta potential, and doping modification, can affect the antimicrobial properties of NPs. NPs with higher roughness can influence bacterial cells and their environment by having a higher surface area, surface energy, and surface charge. Moreover, rougher NPs can generate more ROSs, dissolve faster, and release more metal ions. They can also interact more physically with bacterial cells, depending on the NP type.[3,69] Roberta C. Souza *et al*.[79] used different methods to synthesize ZnO NPs and observed that these changes in synthesis modifications

led to the NP's geometrical alterations and therefore variety in inhibition of bacterial growth. For instance, the sonochemical method versus the classical physicochemical method was used to synthesize ZnO NPs, and the first method showed higher inhibitory properties against *Bacillus cereus*, *Staphylococcus aureus* (*S. aureus*), *Salmonella Typhimurium,* and *Pseudomonas aeruginosa* (*P. aeruginosa*). The physicochemical modification can also affect the antimicrobial activity as it was shown that argon annealing reduced the ZnO NP's antimicrobial activity against *E. coli* and *S. aureus* compared to plasma oxidation.[80]

The zeta potential of an NP is the measurement of electrical charge on the surface. This factor can influence antimicrobial activity by affecting the stability, aggregation, and interaction with bacterial cells or the environment. Based on the negative or positive charge of the bacteria, they can interact more with positive or negative NPs, respectively, and a higher zeta potential charge enhances the electrostatic attraction between NPs and bacteria in addition to producing more ROSs and dissolving faster and releasing more metal ions. This all again depends on the type of NP.[69,81] S Tang and J Zheng used a variety of coated AgNPs in a way that their zeta potential was increased from -38 mV to +40 mV against *Bacillus* spp.[71]

The process of introducing impurity or defects into the crystal structure of NPs is called doping modification. This phenomenon depending on the NP type and dopants has an impact on the band gap, surface charge, surface energy, and catalytic activity of NPs, thus increasing or decreasing generating ROS, dissolving and releasing metal ions, or interacting with the bacterial cells.[82,83]

Environmental factors

Environmental factors and conditions such as pH, temperature, salinity, and the presence of organic matter can also affect the antimicrobial properties of NPs. The acidity or alkalinity of a solution, called pH, can modify the surface charge, solubility, and metal ion release of NPs.[84] For instance, ZnO NPs have higher bacteriostatic action against *S. aureus* and *E. coli* in acidic pH environments than in neutral pH.[69]

Temperature can also influence antimicrobial activity by altering the aggregation and catalytic activity of NPs besides dissolution. It was demonstrated that CuNPs produce more $Cu^{+/2+}$ ions and dissolve faster at higher temperatures, which enhances their antimicrobial activity, while at lower temperatures, they tend to aggregate more and release fewer ions, which reduces their antimicrobial activity. Furthermore, the generation of ROS is higher at higher temperatures, as shown by a study on TiO_2 NPs for antimicrobial activity. However, the catalytic activity and ROS generation are lower at lower temperatures.[84,85]

The amount of dissolved salt or salinity can affect the antimicrobial effect of NPs by changing their stability, aggregation, and interaction with bacterial cells. It was reported that in a highly saline environment, AgNPs aggregate more and their surface charge is neutralized by the salt ions, which lowers their antimicrobial activity, while in a low-salinity environment, they remain stable. Similar results were obtained in Fe oxide NPs.[84] Organic matter also has a similar effect as salinity and can cause changes in NPs' stability, aggregation, solubility, surface charge, and interaction with bacterial cells. For example, ZnO NPs have higher antimicrobial effects in the absence of organic matter.[86]

Green synthesis of NPs

Plant-based NPs (PBNPs) are a class of NPs derived from plant extracts, which act as both reductants and stabilizers. This method presents a more environmentally friendly and safer alternative to conventional techniques involving hazardous chemicals, excessive energy usage, and potential ecological risks. Plant extracts contain an array of phytochemicals, including polyphenols, terpenoids, alkaloids, and flavonoids, capable of reducing metal ions to their elemental state and stabilizing them in aqueous solutions. Under mild conditions, PBNPs can be synthesized by combining plant extracts with metal salt solutions. "Green synthesis" is a method for the preparation of plant extraction with the help of green chemistry that aims to eliminate the use of harmful substances in manufacturing [Figure 3]. The green synthesis process is characterized by simplicity, cost-effectiveness, environmental compatibility, and scalability.[87-89] In the realm of antimicrobial research, PBNPs exhibit diverse applications. They demonstrate exceptional antibacterial,[90,91] antifungal,[91,92] antiviral,[93,94] and antiparasitic properties against a wide range of pathogens.[87,95] Furthermore, PBNPs offer the potential to enhance the effectiveness of antibiotics and address the challenge of drug resistance.[96,97] Additionally, they can function as targeted drug delivery systems, enabling the controlled release of medications at specific infection sites.[98,99] Extensive investigations have demonstrated the antimicrobial capabilities of PBNPs against bacteria (e.g. *E. coli*,[100,101] *S. aureus*, and *P. aeruginosa*),[101] yeasts such as *Candida albicans*[102] and molds such as *Aspergillus flavus*,[103] viruses including HSV and HIV,[93] and parasites (e.g. *Leishmania donovani*[104] and *Plasmodium falciparum*).[105] Noteworthy examples of PBNPs synthesized and assessed for their antimicrobial attributes include AgNPs,[106,107] AuNPs,[91,108]

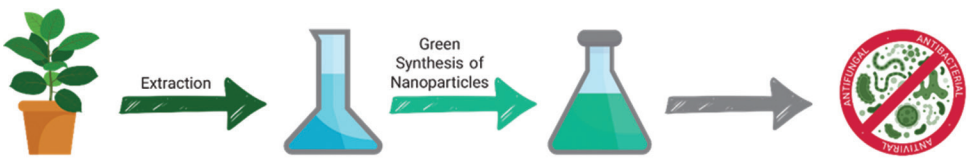


Figure 3: The green synthesis of NPs for antimicrobial applications. This figure illustrates the three steps involved in the green synthesis of NPs from plant extracts: extraction, synthesis, and delivery. The NPs can be used to fight against various microbial infections by targeting them specifically

CuNPs,[109] and TiO_2 NPs.[110,111] These PBNPs have different ways of killing microbes, such as disrupting the cell membrane, blocking the metabolic processes, producing ROS, triggering oxidative stress, and harming the DNA.[112]

Applications

By altering substances' physical, chemical, and biological characteristics, nanotechnology opens up new possibilities for biological applications. Regarding this, several NPs have been found in recent years to be effective against a variety of diseases, including germs that are resistant to antibiotics. NPs can be employed in a number of applications, from antimicrobial synthetic fabrics to biomedical and surgical equipment, when they are implanted, loaded, coated, or applied to various materials.[113] NPs are utilized as nanocarriers for antibiotic administration, antibacterial coatings for implanted devices, medicinal preparations to prevent infections and enhance wound healing, and more.[114,115] Nano-engineering materials are created by altering the surfaces of implants and medical devices to inhibit bacterial adherence and biofilm development. Next-generation NPs for medical implants and devices are affordable and biocompatible antibacterial film-based composite materials that offer a variety of applications, including implant or catheter coatings and wound dressings [Figure 4].[113]

Antibiotic design

Natural and synthetic antibiotics can be resisted by bacteria through various methods;[113,116] due to the difficulty and expense of creating an innovative antibiotic, there is a meager of original antibiotics in the market lately.[117] By leveraging common resistance mechanisms, including inactivating enzymes, lowering cell permeability, changing target sites or enzymes, and boosting efflux through additional efflux pumps, NPs can kill resistant bacteria.[118] NPs can be altered and combined with other antibacterial substances to increase their potency against resistant microbes.[117] NPs' chemical characteristics allow for long-lasting antibiotic adhesion to the target location and protection against enzymes.[119,120] Additionally, NPs and antibiotics work better together to combat bacteria, limit the growth of biofilms, and eliminate multidrug-resistant microorganisms (MDRMs).[118,121] Making antibiotic NP conjugates is important to stop multidrug-resistant harmful microbial infections.

NPs can eradicate bacteria by themselves or can carry conventional antibiotics to the target; in both cases, they are called "nanoantibiotics".[1,114] As a result, they are known as "nanobactericides," while "nanocarriers" are NP-based systems that transport older antibiotics, such as dendrimers, polymeric NPs, metallic NPs, and liposomes, which were the first nanotechnology used for this.[45,122] Nanocarriers are NP-based systems that can carry conventional antibiotics and enhance their properties of absorption and action. NPs are better than conventional antibiotics in many ways, such as killing more types of bacteria, having enhanced effects, resisting resistance mechanisms, and causing a reduction in side effects. To enhance their qualities of absorption/action, antibiotics can be connected, dissolved, wrapped, or confined into nanocarriers.[123]

Hybrid nanosystems of antibiotics

The discovery and availability of nanostructures increased the antibacterial activity of several mineral compounds. Cu, Ag, Au, Zr, and Ti oxides NPs are new antibacterial agents that have been able to solve the problem of MDRMs.[124] Studies suggest that combining metal NPs with antibiotics can improve their bactericidal efficacy.[125] The revealed bacterial effect will lead to a reduction in the required doses and a reduction in the toxicity of both agents for human cells.[126] In addition, the combination of metal NPs with antibiotic drugs preserves their ability to destroy bacteria resistant to them. However, the mechanism of antibiotic activation by metal NPs in hybrid nanosystems is not completely clear. These effects may be due to the high local concentration of antibiotic molecules on the surface of NPs due to their high surface-to-volume ratio, which causes multi-capacitance effects. NPs act in three stages: membrane destabilization, pore formation, and intracellular fluid leakage.[124,127]

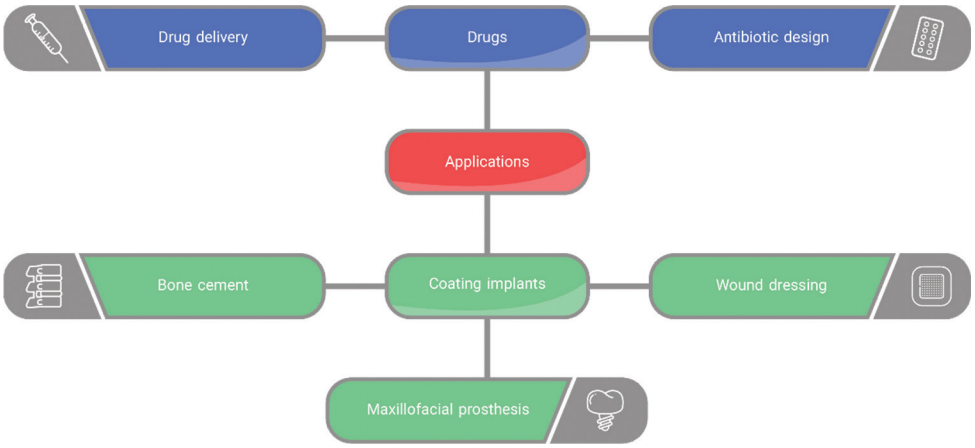


Figure 4: NP applications are divided into two categories: coating implants and medical applications. Drug delivery and antibiotic design are significant in the pharmaceutical sector, while the use of NPs in BC, wound dressings, and maxillofacial prostheses is significant in the coating implants sector

Active antibacterial complexes of metal ions and antibacterial drugs are another possible mechanism of action of hybrid nanosystems based on the formation of antibiotics and metal NPs.[128] The presence of nitrogen and oxygen atoms in the chemical structure of the drug causes electron-donating interactions and ultimately complex formation.[27] Both surface atoms (ions) of NPs and metal ions released from the surface of NPs into the solution can participate in the formation of complexes.[129] Reducing the size and increasing the ratio of surface atoms in NPs may play a role in increasing bacterial activity.[130,131] Hybrid combinations of metal NPs and antibacterial drug molecules can cause an expansion of the bactericidal effectiveness range and restore the activity of antibacterial drugs. In addition to increasing synergy in antimicrobial activity, nanosystems can reduce dose-dependent toxicity, the development of resistance, treatment doses, and the duration of treatment.[126,132]

Drug delivery

NPs have great potential for drug delivery applications. They can be utilized as carriers to deliver pharmaceuticals to particular human tissues or cells.[133,134] By adding reactive groups or molecules, such as antigens to the surface of NPs, the surface chemistry may be changed to target certain cell receptors.[135] Systemically administered cytotoxic drugs can damage the target tissue before reaching it. Low solubility in water and poor pharmacokinetics in the body are weaknesses of synthesized drugs at the global level.[136] To address this issue, NP-based drug delivery systems (NDDSs) have been expanded to deliver therapeutic drugs further efficiently and selectively while avoiding damage to other organs caused by free forms of drugs.[137]

One of the most advanced technologies in the field of NP application is nanoscale drug design, which has many benefits, including the potential for modifying features including immunogenicity, bioavailability, diffusion, drug release patterns, and solubility.[138] Passive and self-delivery are two ways of delivering drugs through nanostructures. Through the hydrophobic effect, drugs are passively integrated into the interior cavity of the structure. In targeting nanostructures to a specific location, desired due to the low concentration of pharmaceuticals contained in a hydrophobic environment, a small quantity of drug is released.[139] In the self-delivery method, the desired drug release is directly conjugated to carrier nanostructured materials for easy delivery. In this method, the time of diffusion is very important because the drug does not reach the desired place or is removed swiftly from the carrier, and vice versa. If it is released from the nanocarrier system at the proper moment, its bioactivity and effectiveness will diminish.[140] In order to increase the pharmacokinetics, stability, and bioavailability of conventional antibiotics as well as their capacity to eradicate bacteria, certain nanomaterials are used as "antibiotic nanocarriers".[141] Nanocarriers enhance antibiotic efficacy and minimize harm by reducing volume distribution, allowing maximum dosage, and causing bacterial cell death at lower concentrations.[134] NPs can be passively or actively targeted at sites of infection. Ligands that bind to diseased tissues or microorganisms as receptors can also be activated on nanocarrier surfaces. This latter approach is known as active targeting or ligand-mediated targeting. These nanocarriers can improve cellular uptake, aiding in intracellular infection treatment.[142,143] Targeted therapy targets intracellular bacteria that would otherwise remain hidden from antibiotics, causing recurrent disease. Passive targeting uses nonspecific ligands, while inactive targeted NPs are selectively released at infection sites with increased blood vessel permeability.[144] Factors such as hydrophobicity, van der Waals forces, and static electrostatic attraction affect delivery efficiency, with electrostatic interactions improving effectiveness.

Another crucial component that makes use of nanomaterials or nanoformulations as drug delivery systems is active or passive drug targeting. In active targeting, drug delivery systems are combined with moieties, like antibodies and peptides. In active targeting, drug delivery systems are combined with moieties, like antibodies and peptides, to attach them to the receptors present in the target area. In passive targeting, the produced complicated drug carrier is carried to the target site through binding or affinity, which depends on variables like pH, temperature, molecular size, and shape as it circulates through the circulation. Membrane-bound receptors on cells, lipids, or proteins on cell surfaces, as well as the cell membrane, make up the majority of the body's targets.[139]

Coating of implants

NPs can be combined with different materials to form bionanocomposites with improved antibacterial capabilities, in addition to solo applications.[145] In this context, experts advise using wound dressings, prostheses, and bone cement as substitutes for conventional treatments and preventative measures for microbial infections.[146,147] Making coatings to create surfaces with antimicrobial and antibiofilm qualities is one of the uses of NPs.[148,149] When it comes to wound care, biomedical problems, and nanomedicine, NPs have the potential to be bactericidal and fungicidal.[150] Wound dressings developed using biocompatible, biodegradable polymers promote healing and protection against infection.[151]

Wound dressing

Polymer-supported NPs for antimicrobial consumer goods, such as hydrogels for wound healing, have been developed.[152] TiO_2 NPs interact with polymers, influencing nanocomposites' chemical and physical characteristics.[153] Zhang *et al*. used in situ-produced TiO_2 NPs in methacrylated gelatin hydrogel films.[154] Implants, wound dressings, and other things benefit from the cleanliness and antibacterial properties of AuNPs.[155] As materials for disinfection, AgNP dressings and solutions are created for cleansing wounds and scrapes.[156]

Bone cement

Bone cement (BC) is a biomaterial commonly used in orthopedic operations to stabilize vertebrae, cure infections, fix prostheses, fill abnormalities, and replace dead spots.[157] Antibiotic-loaded BC has not been found to reduce infection,

according to certain research.[158] When making antibacterial BC, AgNPs are employed in place of antibiotics.[159] The use of metals, particularly Ag, as an antibacterial strategy has demonstrated tremendous potential.[160] BC has been given an Ag^+ ion, which displays antibacterial action without compromising the biomaterial's cytotoxicity.

Maxillofacial prostheses

NPs are an effective therapy for bone infections due to their bactericidal and osteogenic qualities.[161] They can enhance the mechanical properties and antimicrobial effects of maxillofacial prostheses. Metal and metal oxide NPs are effective in treating MDRM infections.[162] NPs such as silicon oxide (SiO_2), TiO_2, Ag, and ZrO_2 enhance dental materials like denture bases, composites, impressions, implants, ceramics, and maxillofacial prostheses.[158] Furthermore, they can modify bacterial metabolism and eradicate resistant microorganisms, such as AgNPs, which can enter biofilms by preventing gene expression.[163] To address microbial colonization that results in biofilms, metal NPs have been directly deposited on the metal implants by electrodeposition.[164]

Present Limitations

Efforts to harness the potential of NPs in fighting drug-resistant bacteria and infections associated with biofilms have garnered significant attention. The need for new therapeutic approaches has accelerated the exploration of NPs' antimicrobial properties. However, despite promising advancements, several challenges and limitations continue to hinder their widespread use in clinical settings. One crucial concern from a regulatory perspective is the safety and potential toxicity of NPs. These tiny particles possess complex physicochemical properties that can lead to unpredictable interactions with biological systems. As a result, a thorough assessment of their potential adverse effects is essential. To assess the possible negative effects of NP exposure on human health and the environment, comprehensive investigations are indispensable.[165] Furthermore, designing and formulating NPs for targeted delivery of antimicrobial drugs remains an ongoing challenge. Achieving controlled release, enhanced stability, and selective targeting while minimizing off-target effects demands sophisticated engineering techniques and a deep understanding of the intricate dynamics between hosts and pathogens.[145,166,167] Another obstacle is the cost-effective large-scale synthesis of NPs with consistent quality and reproducibility. Overcoming these limitations necessitates the standardization of production protocols and the development of efficient fabrication techniques. By doing so, we can address the current challenges related to cost, scalability, and product uniformity.[168,169]

Despite these existing limitations, the future holds promising possibilities for the application of antimicrobial NPs. Innovative strategies, such as combination therapies, synergistic interactions with conventional antibiotics, and surface modifications to enhance stability and targeting, open up exciting avenues for further research. Additionally, advancements in nanotechnology-based delivery systems, including nanocarriers and nanogels, offer prospects for the regulated and prolonged delivery of antimicrobial agents (324-327).[170,171]

NPs resistance

NPs have demonstrated significant potential as antimicrobial agents that can enter the cytoplasmic membranes of pathogenic microorganisms and disrupt crucial molecular pathways.[113] However, the extensive use of NPs may also pose a risk of bacteria developing tolerance to them. This tolerance could undermine their efficacy and further exacerbate the global antibiotic resistance crisis. When referring to NP tolerance, we are indicating the bacteria's capacity to survive or proliferate even when exposed to NPs that would ordinarily inhibit their growth. Various mechanisms enable bacteria to develop tolerance to NPs, such as altering their cell membrane permeability and alternations, efflux pumps, producing antioxidant enzymes, forming biofilms, phage conversion, and horizontally transferring genes. In some instances, NP tolerance can also lead to resistance against antibiotics as the same genes or mechanisms conferring tolerance to NPs can provide resistance against antibiotics as well. For example, the production of multidrug efflux pumps in bacteria induced by AgNPs can reduce the accumulation of both Ag ions and antibiotics within cells.[172-174]

Different mechanisms for resistance in bacteria with different NP treatments have been introduced. For each mechanism, related gene(s) must be expressed. For example, efflux pump genes are *marA, cusFCBA,* and *acrAB-tolC*.[175] Mutation in *purR* and *tcyA* genes leads to resistance in two generations of bacteria.[172] Making changes in structural and non-structural proteins is a way to escape from NP toxicity for bacteria. Changes in YpsA, UgtP, OmpC, OmpF, RodZ, TolC, and SoxS proteins may affect the cell structure and shape of membrane proteins and finally appear in the resistance of bacteria to NPs.[176] A bacterium with one or more applications of the mentioned mechanisms is able to fight NPs and guarantee its life. Changes in DNA for generations and divides, and cell membrane proteins in one generation are employed by bacteria such as *E. coli* for an excellent escape from NPs.

Hence, it is crucial to monitor and inhibit the emergence of bacterial resilience in NPs, particularly in clinical settings where NPs are employed for infection control or treatment. Several strategies can help mitigate the risk of resistance to NPs, such as adjusting the dosage and frequency of NP exposure, combining NPs with other antimicrobial agents such as antibiotics or phytochemicals, and designing NPs that possess multiple modes of action or specifically target bacterial receptors.[176-179] Moreover, further research is necessary to comprehensively comprehend the molecular mechanisms and epidemiology of bacterial resistance to NPs and to develop reliable methods for detecting and characterizing bacteria strains that are resistant to NPs. By doing so, we can guarantee the safe and effective application of NPs as antimicrobial agents, thereby preserving their value for future applications.

Toxicity of NPs for human health

NPs, although effective in their ability to fight germs, deliver drugs, and create diagnostic or therapeutic images, can also pose risks to human health if one is not careful. These tiny particles can enter the body by various routes, such as inhalation, ingestion, dermal contact, or even injection.[180,181] Once inside, they can have a detrimental impact on the cells and organs. In the following section, we will examine the potential toxicity of certain NPs used in medicine.

The level of toxicity of NPs can vary significantly depending on their type and quantity. For instance, AgNPs, while effective at killing bacteria, can also damage cells and genes by releasing destructive agents. AuNPs are generally considered safe, but there are instances where they can trigger immune responses or provoke inflammation.[182,183] SiNPs can transport drugs effectively, but they can also lead to stress and respiratory issues.[184,185] ZnO and TiO_2 NPs offer sun protection, yet if they penetrate the skin, they can cause damage due to the creation of ROS.[186]

Carcinogenesis of NPs has been proven by different studies. Although natural NPs such as extracellular vesicles (EVs) and some synthetic NPs such as SeNP are used for the treatment of cancer and demonstrated antitumor effects,[187] synthetic NPs such as metal-ion-based NPs (CuNP, nickel, and cobalt NPs)[188] are destructive for eucaryotic cells and can cause different cancers in high-dose and long-term exposure. Oxidative stress and ROS in eucaryotic cells are significant threats to their ability to change the signaling peptides, DNA, histones, proteins, and lipids.[189] Enhanced expression of phosphorylated Rad-51, histone H2AX, and p53[190] shows DNA damage and uncontrolled replication of cells after exposure to NPs.

To ensure the safe utilization of NPs in medicine, it is crucial to conduct toxicity tests. This involves examining their properties, understanding the extent and method of exposure, tracking their distribution within the body, and studying how they interact with the molecules. Various models and approaches, such as human cells, animal studies, or computer simulations, allow us to comprehend the potential toxicity of NPs and develop measures to minimize their adverse effects on human health.

Future Perspectives and Growth of Application

NPs are revolutionizing medicine with applications in diagnosis, therapy, drug delivery, and tissue engineering with amazing antimicrobial effects. Antimicrobial feature of NPs in different applications of NPs will be effective and improve the function of NPs. Furthermore, NPs will be the best option for antibiotic design and delivery of antibiotics with enhancing the effect of antibiotics. Their large surface area, small size, and ability to interact with biological molecules overcome the limitations of conventional approaches. NPs also improve drug delivery efficiency and safety by protecting drugs from degradation, enhancing solubility and stability, and facilitating transport across biological barriers. They improve therapeutic effects by increasing drug enrichment at the target site, reducing toxicity and side effects [Figure 5]. NPs enable controlled release and exhibit stimuli-responsive behavior.[166,191] Researchers are exploring ways to design and optimize NPs for various purposes, including green synthesis methods to create eco-friendly NPs from plant extracts[192] and developing multifunctional NPs for simultaneous diagnosis and therapy.[193,194] Integration with technologies like microfluidics,[195] biosensors,[196,197] and artificial intelligence (AI)[198,199] expands their potential. However, challenges like biocompatibility, toxicity, immunogenicity, biodistribution, pharmacokinetics, and pharmacodynamics must be addressed before widespread clinical implementation. Extensive research is essential to establish the safety and efficacy of NP-based medicine. The potential of NPs for medical applications is vast and offers immense potential for the advancement of healthcare. In the near future, we will achieve more success with NPs in medicine due to their incredible activities such as antimicrobial features.

Conclusion

We can find NPs to be beneficial materials that can assist us in dealing with microorganisms in different ways. Elements of NPs, such as size, shape, and other physical and physicochemical properties, are under attention due to their role in antimicrobial features and applications. The potential of NPs in antimicrobial applications in drugs from antibiotics to conjugated compounds for delivery and coating different

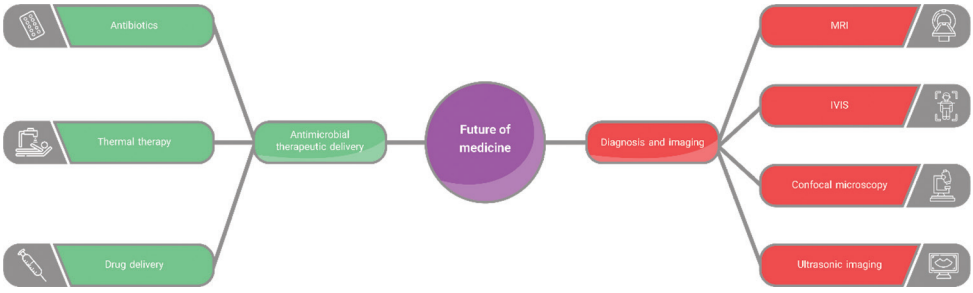


Figure 5: Role of NPs in the future of medicine. NPs can be used for various purposes, such as enhancing the efficacy of antibiotics, delivering drugs to specific targets, providing thermal therapy, and improving the diagnosis and imaging of diseases. This figure shows some examples of how NPs can interact with different biological systems and technologies

implants gives us a better world and life with less microbial role in health and diseases. In the 21st century, our ancient heritages, metals such as Cu, Fe, and Ag, with today's technology and knowledge in nanoscience have shown good results in having a safe world and painless life for humans, especially those who are under surgery or afflicted with infections.

Ethical issues

The Ethics Committee of Bam University of Medical Sciences approved this study (Ethical code # IR.MUBAM.REC.1402.103). The research also followed the tenets of the Declaration of Helsinki. This study was extracted from a research project was conducted in Bam University of Medical Sciences. Additionally, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

Acknowledgments

We have thanks to Bam university of medical sciences for preparing the opportunity for authors to write present review.

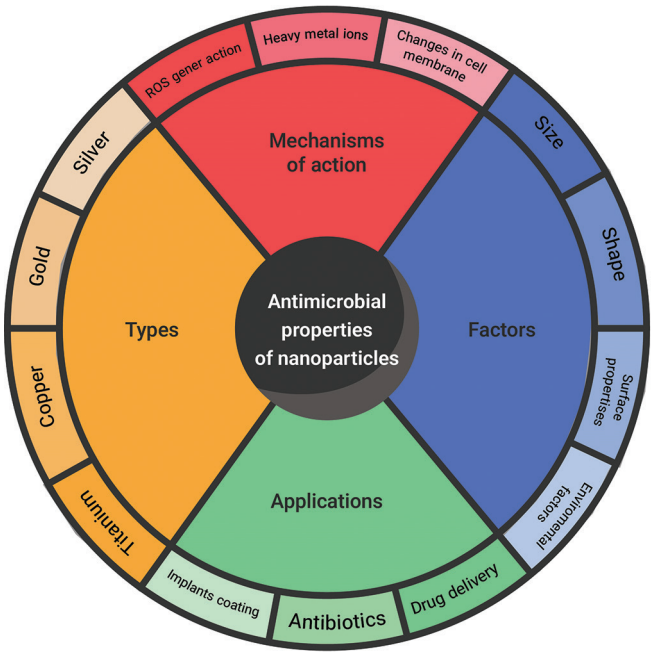
Author contribution

The authors confirm their contribution to the paper as follows: Conceptualization: SMA.MS, and AS, Data curation: H.SZ, SMA.MS, NS, and M.RJ, Formal analysis: SMA.MS, H.SZ, NS, and M.RJ, Project administration: SMA.MS, and AS Supervision: SMA.MS, and AS, Writing–original draft: H.SZ, SMA.MS, NS, M.RJ, and HJ Editing: NS, H.SZ, SMA.MS, and JDG, and Figures design: HJ.

Financial support and sponsorship

This study was supported by Bam University of Medical Sciences, Bam, Iran (Grant # 402000098).

Graphical Abstract



Conflicts of interest

There are no conflicts of interest.

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