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REVIEW PAPER

# Advancements in Nanoparticle-Based Strategies for Enhanced Antibacterial Interventions

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## Abstract

The escalating global threat of antibiotic resistance underscores the urgent need for innovative antimicrobial strategies. This review explores the cutting-edge applications of nanotechnology in combating bacterial infections, addressing a critical healthcare challenge. We critically assess the antimicrobial properties and mechanisms of diverse nanoparticle systems, including liposomes, polymeric micelles, solid lipid nanoparticles, dendrimers, zinc oxide, silver, and gold nanoparticles, as well as nanoencapsulated essential oils. These nanomaterials offer distinct advantages, such as enhanced drug delivery, improved bioavailability, and efficacy against antibiotic-resistant strains. Recent advancements in nanoparticle synthesis, functionalization, and their synergistic interactions with conventional antibiotics are highlighted. The review emphasizes biocompatibility considerations, stressing the need for rigorous safety assessments in nanomaterial applications. By synthesizing current knowledge and identifying emerging trends, this review provides crucial insights for researchers and clinicians aiming to leverage nanotechnology for next-generation antimicrobial therapies. The integration of nanotechnology represents a promising frontier in combating infectious diseases, underscoring the timeliness and imperative of this comprehensive analysis.

**Keywords** Antibiotic resistance · Antimicrobial nanoparticles · Dendrimers · Polymeric nanoparticle · Solid lipid nanoparticles

## Introduction

The emergence of antibiotic-resistant strains and the formation of biofilms that impede the efficacy of antibacterial agents highlight the urgent need for enhanced antibacterial interventions [1]. The ineffectiveness of many antibiotic treatments is often due to unfavorable pharmacokinetic properties of the active compounds, such as limited bioavailability, poor penetration of biological barriers, short half-lives, suboptimal stability, and the development of resistance in patients who are not adequately monitored [2–4]. Current antibiotic strategies are insufficient to address the growing issue of drug resistance, necessitating the development of novel antibacterial agents or the optimization of existing antibiotics through structural modifications [2–4]. Exploring new materials at the nanoscale may offer a path to success.

Nanotechnology, involving the manipulation of materials at atomic or molecular scales, has gained momentum in medical applications, particularly for combating microorganisms. These nanomaterials can be synthesized from a variety of substances, including polymers, lipids, and metals [5, 6]. Materials such as zinc and silver possess inherent

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antimicrobial properties, which are significantly enhanced at the nanoscale due to increased surface-to-mass ratios, offering specific antibacterial mechanisms [7]. Incorporating drugs into nanoparticles (NPs) through physical encapsulation, chemical adsorption, or a combination thereof can markedly improve their pharmacokinetics and therapeutic indices. Nanoparticle-based drug delivery has been investigated for various properties, including improved drug solubility, extended systemic circulation, controlled and stable drug release, targeted delivery to specific tissues and cells, and the simultaneous delivery of multiple drugs. In combination therapy, drug-loaded nanoparticles can enter target cells via endocytosis, enabling the treatment of intracellular infections caused by pathogens. Consequently, certain nanoparticle drug delivery systems have received clinical approval and are currently used to treat specific diseases, with numerous nanoparticle formulations undergoing various stages of clinical trials [8, 9].

NPs can exhibit antimicrobial properties or serve as delivery systems for conventional antibiotics, collectively referred to as "nanoantibiotics." These can be utilized in implantable devices, antibiotic delivery systems, and even antibacterial vaccines [10]. "Nanocarriers" are nanoparticle-mediated delivery systems proposed for administering conventional antibiotics, which can be absorbed, dissolved, encapsulated, or incorporated into nanocarriers to enhance their pharmacological and pharmacodynamic characteristics [11]. However, a comprehensive understanding of the precise mechanisms underlying the antibacterial activity of NPs against bacterial strains remains elusive. One key aspect involves electrostatic interactions, facilitating the attachment of NPs to the bacterial membrane, compromising its structural integrity and causing disruption [12, 13]. The electrostatic interaction between NPs and negatively charged membranes facilitates targeting nanomolecules toward bacteria and enables nanoparticle penetration through the membrane. The highly positive zeta potential of nanomolecules increases the interaction with cell membranes, leading to membrane disruption, bacterial clotting, and reduced viability.

The chemical nature of nanomaterials primarily affects their interaction with cells. Characteristics such as particle size, shape, texture, rigidity, charge, functional groups, and hydrophobicity or hydrophilicity can significantly impact cellular uptake and interactions with cellular components. Multiple endocytic pathways have been identified for nanoparticle internalization into cells, including clathrin-mediated endocytosis, caveolae-dependent endocytosis, passive uptake, and clathrin/caveolae-independent endocytosis [14]. For example, clathrin-mediated endocytosis is a notable pathway for nanoparticle uptake, as inhibiting this route has been shown to reduce cellular nanoparticle uptake. Caveolae-mediated endocytosis is evidenced by the co-localization with caveolin-1 proteins in internalized nanoparticles found within caveolae and caveosomes. Caveolin-mediated endocytosis primarily handles the cellular uptake of nanoparticles ranging from 20 to 100 nm, whereas clathrin-mediated endocytosis predominantly facilitates the uptake of submicron particles ranging from 100 to 350 nm (Fig. 1) [15].

The production of reactive oxygen species (ROS) is a key mechanism of antibacterial activity for nanoparticles [13, 16]. Other mechanisms include DNA degradation during microbial proliferation and cell division, the release of toxic metal ions, and corrosive properties that cause cell lysis [17, 18]. NPs can also function as carriers of antibiotics and other pharmaceutical agents [5, 6]. The mechanism of action of nanoparticles can vary depending on factors such as composition, particle size, inherent properties, and the target bacterium. A targeted approach employing nanoparticles against specific types of bacteria or contaminated tissues offers a more effective strategy, minimizing side effects while enhancing antibacterial activity [19, 20]. Additionally, the use of nanoparticles as antibacterial agents offers the significant advantage of mitigating bacterial drug resistance [21–23]. However, the consumption and release of nanoparticles have raised significant environmental and safety concerns that require further in-depth research [24–26].

In this review, we compile current information on the antimicrobial properties of a range of nanomaterials, including metal antimicrobial NPs, solid lipid NPs (SLNs), dendrimers, liposomes, polymeric micelles, and nanoencapsulated essential oils. The findings of this study could have profound implications in numerous fields, including healthcare, biotechnology, and environmental science.

## Metal Antimicrobial NPs

Metal NPs are extensively employed in medical and healthcare applications, particularly in antimicrobial chemotherapy. Their utility spans various fields, from materials science and electronics to biology and medicine, with metal and metal oxide NPs leading the way. These nanoparticles, typically ranging from 1 to 100 nanometers, exhibit unique physical and chemical properties that distinguish them from their bulk counterparts due to their tiny size and high surface area-to-volume ratio. These nanoscale dimensions, equivalent to assemblies of tens to hundreds of atoms, endow the particles with exceptional characteristics suitable for antimicrobial applications [27]. Metal NPs, primarily composed of pure metal atoms or metal compounds, have been extensively studied and applied in antimicrobial nanotechnology. Among these, silver (Ag), zinc (Zn), and

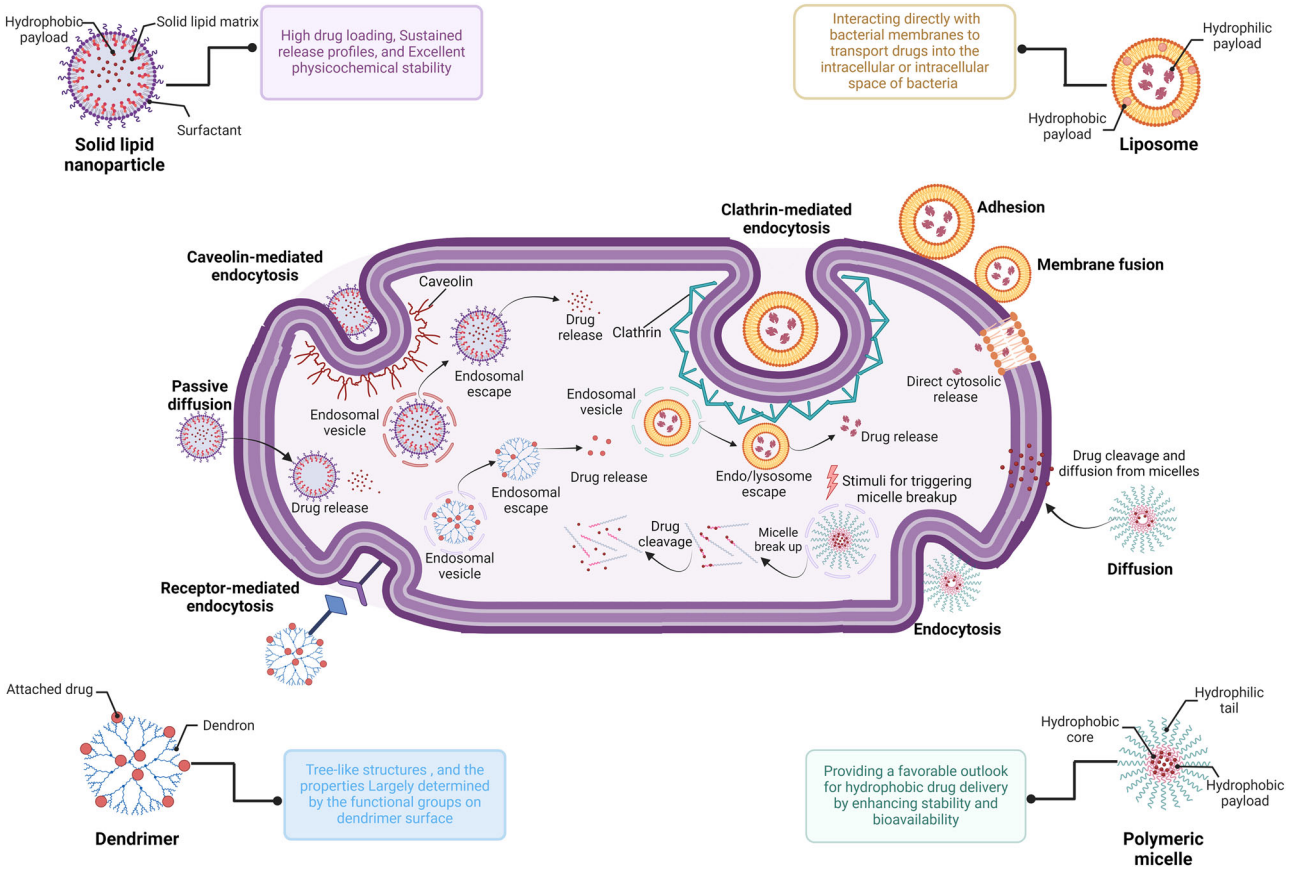


**Fig. 1** Diverse mechanisms of nanocarrier internalization and interaction with cellular components. This figure illustrates the various mechanisms by which nanocarriers, including liposomes, polymeric micelles, solid lipid nanoparticles, and dendrimers, are internalized by cells and interact with cellular components. The interaction and internalization processes are fundamentally influenced by the intrinsic properties of the nanomaterials. Nanocarriers enter cells via multiple endocytic pathways, including clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis, and phagocytosis. Understanding these complex nano-bio interfaces is essential for the rational design of nanocarriers in biomedical applications. This illustration was created using BioRender.com

gold (Au) nanoparticles have garnered significant attention due to their potent antimicrobial activities. These NPs leverage their small size and high surface-to-volume ratio to interact effectively with microbial cells, often disrupting cellular processes through various mechanisms. The enhanced interaction with microbial cell membranes and intracellular components is due to their nanoscale dimensions, which increase reactivity and effectiveness as antimicrobial agents [28]. The unique electronic, optical, and catalytic properties of metal and metal oxide NPs underlie their antimicrobial effectiveness. The versatility of these nanoparticles, in terms of composition and surface modifications, allows for tailored approaches to address specific microbial threats and application requirements. Minerals, including metal nanoparticles such as silver and gold, have demonstrated antibacterial properties even without the use of antibiotics [29]. These nanoparticles exhibit unique characteristics like surface plasmon resonance (SPR), which are absent in liposomes, dendrimers, and micelles, offering advantages such as compatibility and flexibility on surfaces [30]. This adaptability makes them promising candidates for a wide range of antimicrobial applications in healthcare and beyond.

## Silver Nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) possess natural antibacterial properties, particularly effective against Gram-negative bacteria [31]. They inhibit bacterial growth by interacting with bacterial cell membranes and intracellular proteins, disrupting cell division, and causing cell death [7]. When exposed to silver ions, bacterial defense mechanisms involve DNA accumulation to protect against the toxic environment, which, however, compromises the bacteria's ability to multiply [32]. Studies have shown that AgNPs in triangular nanoplate and nanosphere shapes are more effective in reducing the viability of E. coli compared to other shapes like ionic silver nanorods [33]. The antibacterial activity of triangular particles is attributed to their positive charge and increased electrostatic interactions with

bacterial cells [34]. The binding of AgNPs to the negatively charged parts of the microbial membrane creates holes in the membrane, allows the cytoplasmic content to leak out, disrupts the H+ gradient in the membrane, and ultimately causes cell death. Additionally, AgNPs release Ag+ ions, which further exert antimicrobial effects within the bacterial cytoplasm [35, 36]. Gram-negative bacteria are more sensitive to Ag+ ions than Gram-positive bacteria due to differences in their cell wall structures. Gram-negative bacteria have a thinner cell wall than Gram-positive bacteria, allowing $Ag^{+}$ ions to easily enter the bacterial cell. However, Ag+ might bind more strongly to the lipopolysaccharides (LPS) of the outer membrane of Gram-negative bacteria and become trapped in the LPS layer [36, 37].

AgNPs exhibit various mechanisms to kill microbes, including altering membrane permeability, inhibiting cytochromes involved in electron transfer chains, affecting the activity of biological molecules by interacting with their sulfhydryl groups, inhibiting cell wall synthesis in Gram-positive bacteria, preventing DNA transcription, denaturing ribosomal subunits, inhibiting protein synthesis, and producing reactive oxygen species. AgNPs also possess plasmonic photothermal properties, allowing them to convert light into heat energy, further enhancing their antibacterial activity [38, 39]. AgNPs can be utilized in wound healing due to their ability to stimulate fibroblast proliferation and differentiation into myofibroblasts, as well as keratinocyte proliferation and displacement [40].

Numerous in vitro studies have demonstrated that AgNPs are effective as nano-antibacterial agents against a wide range of bacteria. They can also synergize with various antibiotics, enhancing their effectiveness against both sensitive and resistant strains. In one of the initial studies, the minimum inhibitory concentration (MIC) levels of AgNPs and amoxicillin were examined individually and in combination against *E. coli*. The MIC level for AgNPs alone was 40 µg/ml, while for amoxicillin alone, it was 0.525 mg/ml. However, when combined, their MIC levels significantly decreased, suggesting a synergistic effect that improves antibacterial efficacy against *E. coli*. This synergistic effect may occur through various mechanisms, such as targeting different bacterial elements, forming chelate complexes between AgNPs and antibiotics, and facilitating antibiotic transport. Durán et al. discovered a significant link between amoxicillin and silver nanoparticles, termed sulfur bridges, leading to high concentrations of antibiotics [22, 41]. Despite their effectiveness, AgNPs present challenges for whole-body infection treatment and are primarily used in medical coatings, surgical materials, wound healing, and topical antimicrobial formulations [42]. Table 1 summarizes reports on the antibacterial properties of AgNPs.

**Table 1** Summary of select studies concerning the antimicrobial effects of AgNPs

| Size data | Organism Tested | Minimum Inhibitory Concentration | Proposed Mechanism | Reference |
|---|---|---|---|---|
| 12 nm | *Escherichia coli* | 70% reduction at 10 µg/mL | Membrane degradation; Ag ion interference in DNA replication | [19] |
| 13.5 nm | *Staphylococcus aureus*; *Escherichia coli* | 3.56 µg/L and 0.356 µg/L, respectively, on agar surface | Membrane degradation; Ag ion interference in DNA replication | [24] |
| 21 nm | *Escherichia coli*; *Vibrio cholera*; *Salmonella spp.*; *Pseudomonas aeruginosa* | All reduced 100% at 75 µg/mL | Membrane degradation; Ag ion interference in DNA replication | [31] |
| Triangles (50 nm) | *Escherichia coli* | 99% reduction with 0.1 µg/mL on agar surface | Membrane degradation; Ag ion interference in DNA replication | [34] |
| 14.1–710 nm | *Bacillus subtilis* | 76% CFU reduction by applying silver nanoparticles aerosol on *B. subtilis* aerosol | Membrane degradation; Ag ion interference in DNA replication | [163] |
| 1–10 nm | *Pseudomonas aeruginosa* | 25–100 mg/l | Impairs permeability, respiration, and cell division; binds to cell membranes and compounds containing sulfur and phosphorus | [31] |
| ~10 nm | *Pseudomonas putida* | 1 mg/l | Membrane degradation | [164] |
| 5–100 nm | Waste water biofilm-forming bacteria | 1–200 mg/l | Removal of EPS enhances susceptibility to Ag-NPs; bacterial membrane and cell destruction | [165] |

## Gold Nanoparticles (AuNPs)

Gold nanoparticles (AuNPs) come in various sizes and shapes, such as nanospheres, nanorods, nanoparticles, and nanocells. These factors significantly influence their properties, including color. For instance, nanospheres appear ruby red, while other nanoparticle shapes can be blue or black [43]. AuNPs are utilized in various biomedical fields, including biosensors, genomics, targeted cancer therapy through heat and light, and combating microbial infections [44]. They have a wide range of applications as nano-antibacterial agents and nanocarriers for antibiotics [45]. However, there are conflicting opinions regarding the inherent antibacterial activity of AuNPs. Most scientists argue that AuNPs alone do not possess intrinsic antibacterial properties and cannot be considered standalone nano-antibacterial agents [22, 46]. Nonetheless, studies have shown that gold nanoparticles can effectively inhibit the growth of various bacteria and fungi [47]. AuNPs have been used as carrier systems for antibiotics such as streptomycin, gentamicin, and neomycin, exhibiting strong antibacterial effects against both Gram-negative and Gram-positive bacteria like *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Micrococcus luteus*. Additionally, metal nanoparticles may alter metabolic pathways and ion release mechanisms in bacterial cells, further enhancing their antibacterial performance [48].

In-depth investigations have revealed various mechanisms by which AuNP-drug compounds enter microorganisms and exert their effects. Small-angle X-ray scattering analysis confirmed that AuNP compounds attach to and penetrate bacterial cell walls, disrupting the cellular environment and leading to cell lysis and leakage of cellular components [49]. Researchers have found that AuNPs inhibit tRNA binding to ribosomes, disrupt protein synthesis, decrease ATP synthase activity, reduce ATP levels, and alter electrochemical gradients and membrane potential [50, 51]. Unlike most metal nanoparticles, AuNPs do not generate ROS, making them potentially less toxic to mammalian cells.

In 2003, Goo et al. were pioneers in utilizing vancomycin-AuNPs for drug delivery, demonstrating enhanced activity compared to free vancomycin, effectively killing vancomycin-resistant Enterococci (VRE) and *E. coli* strains [52]. One study utilized ampicillin to prepare ampicillin-coated gold nanoparticles (Amp-AuNPs). Amp-AuNPs accumulated on the bacterial surface, creating pores in the membrane through which they entered the cells. Amp-AuNPs exhibited efficacy against ampicillin-resistant *E. coli* and, due to their strong adhesion properties, interfered with biofilm formation [53]. Despite ongoing debates regarding the use of gold as an antibacterial agent, AuNPs are recognized as ideal nanocarriers for a variety of molecules, including vaccines, antimicrobial peptides, and conventional antibiotics. They have been successfully utilized for drug delivery, demonstrating increased efficacy compared to free drugs [54].

## Zinc Oxide (ZnONPs)

Zinc oxide NPs (ZnONPs) possess natural antibacterial properties and have been effectively employed to combat bacterial infections [55]. Although the exact mechanism of action of ZnONPs is not fully understood, it is believed to involve interactions between NPs and water and oxygen molecules on their surface, leading to the formation of highly reactive species such as superoxide anion (O2−), hydrogen peroxide (H2O2), and hydroxyl radical (OH−) [56]. The antibacterial activity of ZnONPs operates through multiple mechanisms. One key mechanism is direct ROS-mediated damage, where the generated ROSs induce oxidative stress in bacterial cells, causing lipid peroxidation, protein oxidation, and DNA damage [57]. Additionally, ZnONPs can disrupt bacterial cell membranes, causing structural changes and increasing permeability, which facilitates the entry of ROS and $Zn2^{+}$ ions into the cells [58]. The dissolution of ZnONPs further releases $Zn2^{+}$ ions, which interfere with bacterial metabolism and contribute to ROS production [59].

The role of ROS and reactive nitrogen species (RNS) modulation in the antimicrobial mechanisms of metal and metal oxide nanoparticles, including ZnONPs, is crucial. This modulation enhances antibacterial effects through synergistic oxidative and nitrosative stress, overwhelming bacterial antioxidant defenses more effectively than either species alone. Additionally, the reaction between O2− and nitric oxide (NO−) produces peroxynitrite (ONOO−), a highly reactive species with potent antimicrobial properties. ROS and RNS also disrupt bacterial cell signaling pathways, affecting various cellular processes and potentially enhancing the overall antibacterial effect [60].

Studies have demonstrated that ZnONPs exhibit bactericidal properties against *Bacillus subtilis*, *E. coli*, *S. Typhi*, and *S. aureus* [61]. Under ultraviolet (UV) radiation exposure in aqueous solutions, ZnONPs generated ROS, including $H_2O_2$ and superoxide ions ($O_2^-$), which were effective in targeting microbes [62]. Raghupathi et al. reported that ZnONPs' remarkable antibacterial efficacy was attributed to enhanced ROS production in the presence of UV light [63]. The toxicity of ROS is directly linked to damage inflicted on cellular components such as lipids, nucleic acids, and proteins through ROS internalization. Nonetheless, some studies have observed ROS production even in the absence of light [64]. ZnONPs have shown inhibitory effects on methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), and methicillin-resistant *S. epidermidis* (MRSE)

**Table 2** Summary of select studies concerning the antimicrobial effects of ZnONPs

| Size (average) | Organism Tested | Minimum Inhibitory Concentration | Proposed Mechanism | Reference |
|---|---|---|---|---|
| 12 nm | *Escherichia coli* | 90% reduction at 400 µg/mL | Particle abrasive membrane damage | [166] |
| 13 nm | *Staphylococcus aureus* | 95% reduction at 80 µg/mL | ROS inhibition | [71] |
| 40 nm | *Staphylococcus aureus* and *Escherichia coli* | 99% reduction at 400 µg/mL | Membrane disruption | [167] |
| 60 nm | *Staphylococcus aureus* | 50% reduction at 400 µg/mL | ROS inhibition | [168] |
| 50–70 nm | *Pseudomonas putida* | 90% reduction at 10 mg/l | Inhibition of bacterial growth | [164] |
| 25–40 nm | *Salmonella typhimurium* | 50% reduction at 80 ng/ml | ROS inhibition | [169] |
| 8–15 nm | *Pseudomonas aeruginosa* | 90% reduction at 10 mg/ml in 16 h | Antimicrobial activity through nitrification of protein sulfur and nitrosylation of metal centers | [170] |
| <100 nm | *(Halophilic) bacterium spp.* | 90% reduction at 2 or 5 mM | Electrochemical membrane alteration | [171] |

strains, emerging as effective antibacterial agents unaffected by drug-resistant mechanisms exhibited by MRSA and MRSE [65, 66]. ZnONPs are relatively inexpensive and exhibit broad-spectrum antibacterial activity, targeting pathogens such as *Klebsiella pneumoniae* [67], *Listeria monocytogenes* [68], *Salmonella* spp., *Streptococcus mutans*, and *E. coli* [69, 70], while exhibiting low toxicity towards human cells [71]. Table 2 presents a summary of additional findings from reported studies. Therefore, the antibacterial activity of ZnONPs is intricately linked to their ability to generate ROS and modulate ROS/RNS levels. This multifaceted approach contributes to their efficacy against a wide range of bacterial pathogens and underscores their potential in various biomedical applications.

## NPs as Delivery Systems for Antimicrobial Activity

The efficacy of antimicrobial NPs is significantly influenced by their delivery systems, which play a crucial role in enhancing bioavailability, targeting specificity, and controlled release. Among the diverse array of nanocarriers, liposomes, solid lipid nanoparticles (SLNs), and dendrimers have emerged as promising platforms for antimicrobial NP delivery [72, 73]. Liposomes, with their phospholipid bilayer structure that mimics cell membranes, offer excellent biocompatibility and the ability to encapsulate both hydrophilic and hydrophobic antimicrobial agents. This versatility allows for the efficient delivery of a wide range of drugs, enhancing their stability and bioavailability. Additionally, the surface of liposomes can be modified with targeting ligands to improve specificity towards microbial pathogens, thereby reducing off-target effects and potential toxicity [74]. Solid lipid nanoparticles (SLNs), composed of lipids that are solid at body temperature, provide stability and sustained release capabilities. This characteristic can potentially reduce dosing frequency and improve therapeutic outcomes by maintaining consistent drug levels in the body over extended periods. The solid matrix of SLNs protects the encapsulated antimicrobial agents from degradation, enhancing their shelf-life and therapeutic efficacy [75, 76]. Dendrimers, highly branched and symmetrical macromolecules, offer precise control over size, shape, and surface functionality. This structural precision enables tailored interactions with microbial pathogens and enhanced penetration of biofilms, a critical factor in treating chronic and biofilm-associated infections. Dendrimers' multivalent surface can be functionalized with multiple antimicrobial agents or targeting moieties, further increasing their potency and specificity [77, 78].

Each of these delivery systems presents unique advantages in terms of drug loading capacity, stability, and targeting potential. They address challenges such as poor solubility, rapid clearance, and off-target effects often associated with conventional antimicrobial therapies. The selection and optimization of these nanocarriers for specific NPs and target pathogens represent a critical area of research in the ongoing battle against antimicrobial resistance. The integration of advanced nanocarrier systems such as liposomes, SLNs, and dendrimers with NPs holds significant promise in enhancing the therapeutic efficacy of antimicrobial agents. Continued research and development in this field are essential to overcoming the limitations of

traditional antimicrobial therapies and addressing the growing challenge of antimicrobial resistance.

## Liposome-Based Antimicrobial Delivery

Liposomes are spherical lipid vesicles with a bilayer membrane structure composed of dual lipid molecules. Their structure was first described in 1965, and they were explored as nanoparticle carriers for drug delivery in the 1970s [79]. Liposomes can be made from natural or synthetic fats, with phosphatidylcholine being one of the most commonly used lipids. Phosphatidylcholine is an electrically neutral phospholipid with fatty acyl chains of varying saturation and length. Cholesterol is often included to regulate membrane strength and stability [80]. Structurally, liposomes are divided into two groups: multilamellar vesicles (MLV), composed of multiple phospholipid layers, and unilamellar vesicles (ULV), consisting of a single lipid bilayer. ULVs are further classified into small unilamellar vesicles (SUV), large unilamellar vesicles (LUV), and giant unilamellar vesicles (GUV) based on their size range [81, 82]. Each type of liposome has distinct characteristics, advantages, and disadvantages for drug encapsulation. Liposomes, with their lipid bilayer surrounding an aqueous core, allow for the encapsulation of both hydrophobic and hydrophilic compounds, eliminating the need for chemical alterations. Furthermore, the surface of liposomes can be coated with "stealth" materials to enhance their stability within the body or functionalized with targeting ligands to facilitate selective delivery and prolonged circulation in the bloodstream [83, 84].

Recent advancements in the functionalization of liposomes and nanoliposomes for antimicrobial applications have significantly broadened their potential across the pharmaceutical, cosmetic, and nutraceutical industries. These versatile drug delivery systems can be prepared using both traditional and innovative methods, each offering distinct benefits and drawbacks. Conventional techniques such as thin-film hydration, reverse-phase evaporation, and ethanol injection are commonly used but often face challenges with controlling size distribution and encapsulation efficiency [56, 85].

To overcome these limitations, novel methods have been developed, including microfluidic techniques, supercritical fluid methods, and membrane contactor technology. These cutting-edge approaches provide improved control over liposome characteristics, enhanced reproducibility, and scalability for large-scale production. Numerous large-scale techniques for producing liposomes with antimicrobial properties have been detailed, focusing on optimizing methods such as thin-film hydration, ethanol injection, and microfluidization to enhance mass production. Surface modification strategies, such as modification of proteins with polyethylene glycol (PEGylation) and the incorporation of targeting ligands, have enhanced the stability and specificity of these nanocarriers. Additionally, incorporating antimicrobial peptides and essential oils into liposomal formulations has shown promise in combating drug-resistant pathogens [86, 87].

The choice of preparation method greatly influences the final properties of liposomes and their suitability for specific therapeutic applications. Factors affecting this decision include lipid composition, desired size range, and intended use. The scalability of these techniques, combined with their ability to maintain the biological activity of encapsulated substances, positions functionalized liposomes and nanoliposomes as versatile platforms for developing advanced antimicrobial products across various sectors. A notable example is the phospholipid-based approach for reversing natural drug resistance in Gram-negative bacteria, as reported by Liu et al. Their study demonstrated the efficacy of a fusidic acid-phospholipid complex (FA-PC) against resistant strains like *E. coli* and *P. aeruginosa*. The FA-PC improved fusidic acid's water solubility from 5 µg/mL to 133 µg/mL and achieved a 99.9% viability loss in *E. coli* after 6 h of treatment. This innovative strategy highlights the potential of phospholipid-based systems in combating antibiotic resistance and warrants further exploration in clinical settings [88]. By interacting directly with bacterial membranes, liposomes can transport drug cargoes into the intracellular space of bacteria. Their PEG coating induces a hydration layer that hinders hydrophobic and electrostatic interactions with plasma proteins, thereby delaying detection by the reticuloendothelial (RES) system. Ligands such as antibodies, antibody fragments, aptamers, peptides, and small molecule ligands can be attached to liposomes to selectively target infected microorganisms or cells and release drug payloads to enhance therapeutic efficiency [83, 84]. Table 3 provides a summary of research investigations employing liposome-based systems for antibacterial drug delivery purposes.

## Solid Lipid Nanoparticles (SLNs) for Antimicrobial Delivery

Since the 1990s, SLNs have gained popularity as an effective platform for antimicrobial delivery. These particle systems, with diameters ranging from 50 nm to 1000 nm, are composed of solid lipids and surfactants to stabilize emulsions. The formulation of SLNs includes various solid lipids such as fatty acids, triglycerides, steroids, partial glycerides, and waxes. Emulsifiers like lecithin, phosphatidylcholine, poloxamer 188, sodium cholate, and glycolate are used to stabilize lipid dispersion [89]. SLNs have proven to be effective for topical applications due to their ability to form a layer that prolongs drug retention in the stratum corneum.

**Table 3** Liposomes-based antibacterial drug delivery systems

| Drug | Composition | Target microorganism | Activity | References |
|---|---|---|---|---|
| Amphotericin B | Hydrogenated soy phosphatidylcholine; and cholesterol | *Aspergillus fumigatus* | Targeted drug delivery at infection site | [82, 172, 173] |
| Polymyxin B | Hydrogenated soy phosphatidylcholine; and cholesterol | *Pseudomonas aeruginosa* | Decreased bacteria count in lung; increased bioavailability | [174, 175] |
| Ampillicin | Cholesterol | *Micrococcus Luteus* and *Salmonella typhimurium* | Complete biological activity; reduced animal mortality | [176] |
| Netilmicin | Phosphatidylcholine; cholesterol; and phosphatidylinositol. | *Escherichia coli* and *bacillus subtilis* | Reduced toxicity; increased stability in animal models | [177] |
| Ciprofloxacin | Dipalmitoyl-phosphatidylcholine; dipalmitoyl-phosphatidylglycerol; and cholesterol. | *Salmonella dublin* | Reduced mortality in animals; distribution of liposomes throughout infection sites | [178] |
| Benzyl Penicillin | Dipalmitoyl-phosphatidylcholine and cholesterol | *Staphylococcus aureus* | Lower concentration and shorter exposure time compared to the drug alone | [179] |
| Gentamicin | Partially hydrogenated egg phosphatidylcholine and cholesterol | *Klebsiella pneumonia* | Increased stability in animal models; enhanced therapeutic effect | [180] |
| Amikacin | Hydrogenated soy phosphatidylcholine and cholesterol | Gram-negative bacteria | Increased antimicrobial activity; prolonged drug exposure | [181] |
| Vancomycin or Teicoplanin | Phosphatidylcholine; diacetylphosphate; and cholesterol | MRSA | Increased intracellular antimicrobial effect | [182] |

They are particularly useful for delivering azole antifungal drugs to patients with superficial fungal infections. SLNs with a small particle size (around 150 nm) have demonstrated increased drug delivery rates in deeper layers of the skin. Clotrimazole and ketoconazole SLNs exhibit high drug loading, sustained release profiles, and excellent physicochemical stability [90, 91]. In addition to topical use, SLNs can be formulated into tablets, capsules, and pellets for oral administration [92]. For example, in the case of tobramycin, an oral antimicrobial drug, SLNs have shown potential in inhibiting the P-glycoprotein efflux pump, thereby enhancing drug uptake by intestinal cells. By entering through endocytosis and bypassing active transport mechanisms, SLNs release tobramycin loads into cells, leading to increased efficacy against bacteria [93, 94]. A combination of drugs, including rifampicin, isoniazid, and pyrazinamide, has been incorporated into SLNs using stearic acid to target Mycobacterium tuberculosis. This composition offers multiple benefits, including increased shelf life, improved bioavailability of the drug, and a reduction in dosing frequency [95]. In another study, ciprofloxacin hydrochloride was combined with stearic acid, soya phosphatidylcholine, and sodium taurocholate to target both Gram-negative and Gram-positive bacteria, resulting in long-term drug release [96]. Additionally, tobramycin combined with stearic acid, soya phosphatidylcholine, and sodium taurocholate was formulated to combat *P. aeruginosa*, focusing on increasing the drug's bioavailability [97]. Furthermore, the formulation of econazole nitrate with glycerol palmitostearate demonstrated high efficiency in capsule production and enhanced drug penetration through the stratum corneum for targeting fungi [98].

## Dendrimers for Antimicrobial Delivery

Dendrimers are precisely synthesized spherical macromolecules, initially introduced by Tomalia in 1984 with polyamidoamine (PAMAM) dendrimers (Generation 1 poly(amidoamine)), which have since gained prominence [99]. These dendrimers exhibit unique properties depending on their structure and functional groups. Anionic amphiphilic dendrimers disrupt prokaryotic membranes, suggesting potential antibacterial activity with minimal cytotoxicity to eukaryotic cells. In contrast, cationic dendrimers have shown cytotoxic effects on eukaryotic cell lines [100]. Silver dendrimer complexes are particularly studied for their antimicrobial properties. For example, (PAMAM) G3 dendrimers modified with AgNO3 or MesoSilver form metal nanoparticles, demonstrating broad-spectrum antimicrobial activity [101]. Dendrimer biocides with quaternary ammonium salts as functional end groups disrupt bacterial membranes through electrostatic adsorption, increasing membrane permeability and leading to bacterial membrane

disintegration [102]. Combination strategies involving PAMAM dendrimers with various drugs have been explored to enhance their efficacy. For instance, nadifloxacin and prulifloxacin formulated with PAMAM dendrimers exhibit increased water solubility and improved effectiveness against diverse bacterial strains [103]. Silver salt complexes with PAMAM dendrimers have shown prolonged circulatory half-life and efficacy against Gram-positive bacteria such as *S. aureus*, *P. aeruginosa*, and *E. coli*. Sulfamethoxazole, delivered via PAMAM dendrimers, enables sustained drug release, enhancing antibacterial activity against pathogens like *S. aureus* and *Haemophilus influenzae* [104].

## Biopolymer-Based Antimicrobial NPs

Biopolymeric nanoparticles have emerged as a promising platform for antimicrobial applications, offering unique advantages in combating pathogenic microorganisms. Among natural polymers, chitosan has garnered significant attention due to its intrinsic antibacterial activity, biocompatibility, and biodegradability. Recent studies have demonstrated the versatility of chitosan-based nanosystems in combating bacterial infections [105].

### Chitosan-Based Nanosystems

Chitosan, derived from the deacetylation of chitin, is a linear polysaccharide that has become a cornerstone in antimicrobial nanotechnology. Its antibacterial properties stem from several mechanisms, including membrane disruption, chelation of essential trace elements, and inhibition of mRNA synthesis, making it effective against a broad spectrum of pathogens [106]. Nanoformulation strategies have significantly enhanced chitosan's antimicrobial efficacy. For example, Tan et al. developed chitosan-based nanocarriers capable of penetrating bacterial biofilms, thereby improving the delivery and efficacy of encapsulated antibiotics [107]. This approach is crucial in addressing biofilm-associated infections, which are notoriously resistant to conventional treatments. Research has also explored synergistic combinations of chitosan with other antimicrobial agents. Wang et al. demonstrated that chitosan nanoparticles loaded with silver ions exhibit enhanced antibacterial activity against both Gram-positive and Gram-negative bacteria, leveraging the complementary mechanisms of action between chitosan and silver ions [108]. Surface modification techniques have further expanded the utility of chitosan nanoparticles. Geng et al. functionalized chitosan nanoparticles with targeting ligands, enhancing their specificity towards bacterial cells while minimizing cytotoxicity to mammalian cells [109]. This targeted approach holds promise for improving the precision of antimicrobial therapies. Beyond direct antimicrobial applications, chitosan nanoparticles serve as effective carriers for antimicrobial peptides, enhancing their stability and prolonging their activity [110]. Additionally, they have been tailored for intracellular drug delivery, facilitating the treatment of persistent infections caused by intracellular pathogens. The biocompatibility and biodegradability of chitosan make it environmentally friendly and suitable for various applications, including food packaging materials aimed at extending shelf life and ensuring food safety [111]. Ongoing research focuses on optimizing chitosan nanoparticles' physicochemical properties, such as molecular weight and degree of deacetylation, to further enhance their antimicrobial efficacy and biocompatibility. Hence, chitosan-based nanosystems represent a promising frontier in antimicrobial research, offering a versatile platform for developing effective and biocompatible antimicrobial strategies. As antimicrobial resistance continues to challenge global health, these innovative approaches hold potential for advancing next-generation antimicrobial therapies.

### Polymeric Micelles Nanosystems

Polymeric micelles are nanostructures formed by amphiphilic block copolymers that self-assemble into core-shell structures in aqueous environments. The hydrophobic core can encapsulate hydrophobic drugs, while the hydrophilic shell ensures solubility and stability in water, preventing rapid excretion and promoting biocompatibility. Typically less than 100 nm in size, polymeric micelles possess a narrow size distribution that aids in avoiding quick excretion and enhances their stability and bioavailability for hydrophobic drug delivery. The concept of polymeric micelles as drug delivery systems was pioneered in 1984, leading to the development of doxorubicin-loaded block copolymeric micelle formulations several years later. Today, poly(ethylene oxide)-poly(propylene oxide) (PEO-PPO) block copolymers are commonly employed due to their FDA approval. Polyethylene glycol (PEG) is often used as the hydrophilic component, contributing to the micelles' stability in vivo by reducing excretion rates [112, 113].

Recent studies have explored various drugs and polymers for their effectiveness against different microorganisms. For example, pyrazinamide, isoniazid, and rifampicin, when combined with PEG-poly (aspartic acid) polymer, demonstrated significant efficacy against *Mycobacterium tuberculosis*, with a minimal inhibitory concentration (MIC) 5.6 times lower than traditional treatments [114]. Similarly, doxycycline and streptomycin, combined with PEO-b-PAA$-Na^+$ polymer, have been investigated against *Brucella melitensis* 16 M, although specific MIC values were not reported [115].

Vancomycin, combined with the poloxamer Pluronic F127 polymer, showed effectiveness against *S. aureus* at a concentration of 1 mg/L [116]. Additionally, pyrazinamide combined with PEG-PASP polymer exhibited variable MIC values against Ra-*M. tuberculosis* (≤6.25 mg/L) and Rv-*M. tuberculosis* (12.5 mg/L) [115]. These findings underscore the potential of polymeric micelle-based drug delivery systems in targeting specific microorganisms and enhancing the efficacy of antimicrobial therapies. By optimizing drug-polymer combinations, polymeric micelles can be tailored to address various microbial infections, presenting a promising avenue for advanced antimicrobial treatment strategies.

## Nanoencapsulated Essential Oils

Recent advancements in science have sparked significant interest in the medicinal properties of plants due to their low toxicity, potent medicinal effects, and economic viability [117]. Essential oils (EOs), naturally derived compounds from plants, have gained attention for their antioxidant and antimicrobial properties when added to food [118]. EOs are produced through intricate metabolic pathways in plants, serving protective functions such as preventing pathogens and insects, and discouraging herbivores by imparting an unpleasant taste [119]. Derived from aromatic and medicinal plants, EOs have shown inhibitory effects on free radicals and are being explored as potential herbal medicines [120]. Besides their application in industries such as soap, perfume, and cosmetics, EOs have a long history of use in traditional medicine [121, 122]. Their demonstrated antifungal, antibacterial, and antiviral properties make them valuable for food preservation and the treatment of infectious diseases. This diverse bioactivity can be attributed to the complex and varied chemical composition of Eos [123–125]. The composition can be influenced by factors such as the plant parts used for extraction, the season of harvest, and environmental conditions, necessitating careful cultivation practices [126].

Os consist of complex mixtures of natural compounds that vary among different plant species. Their hydrophobic nature allows them to integrate with the lipids in bacterial and mitochondrial cell membranes, altering cellular structures and making them more permeable, leading to the leakage of vital molecules and ions, and ultimately resulting in bacterial cell death [127, 128]. EOs primarily consist of terpenes and their derivatives, with oxygenated compounds contributing to their taste and scent. Monoterpenes, sesquiterpenes, and diterpenes are the major constituents of EOs found in various plant cells. Monoterpenes are particularly advantageous for their ability to diffuse through cell membranes and skin layers, enhancing the delivery of pharmaceutical substances [129, 130]. Furthermore, the hydrophobicity and short carbon chains of EO constituents enable them to disrupt microbial cell membranes and inhibit specific proteins. EO compounds also demonstrate phyto-synergistic interactions, enhancing the efficacy of other antibiotics and reducing the likelihood of resistance [125, 131–133].

EOs have shown remarkable antimicrobial properties against bacteria, yeasts, and fungi in both in vitro and in vivo studies [134]. Pathogenic strains resistant to multiple antibiotics, such as *S. aureus*, *Salmonella* spp., *Shigella* spp., coagulase-negative staphylococci, enterococci, *E. coli*, and *P. aeruginosa*, have been effectively targeted by EOs [131].

The nanoencapsulation of essential oils using nanoparticles has emerged as a promising strategy to enhance their antibacterial effects. Nanocarriers can protect essential oils from degradation, increase their stability, and improve their antimicrobial activity through controlled release and diverse diffusion properties [135]. This approach shows potential for overcoming the limitations of essential oils in terms of shelf life and application. Several studies have investigated the transportation of essential oils using nanoparticles, providing valuable insights into this field [135]. Table 4 summarizes results and reports from several studies investigating the use of nanoparticles for the antimicrobial delivery of essential oils.

Further research has compared the antimicrobial activity of free EOs with encapsulated EOs using nanoparticles. Findings indicate that the encapsulation of EOs in nanoparticles not only retains the inhibitory doses but also improves other properties such as controlled release and reduced cytotoxicity [136]. This is particularly beneficial for polymer nanoparticles loaded with antimicrobial EOs, as it reduces the cytotoxic effects on mammalian cells. Additionally, carvacrol-containing poly (lactic-co-glycolic acid) (PLGA) nanocapsules have shown a significant impact on bacterial biofilms, enhancing the antimicrobial properties of essential oils. Encouraging results have been observed with micro- and nanoemulsions of essential oils [137].

In the food industry, nanoemulsions prepared using sunflower oil have exhibited activity against various pathogens such as *Salmonella* spp., *L. monocytogenes*, *S. aureus*, *Aspergillus niger*, and *Penicillium* sp. These nanoemulsions have demonstrated significant antimicrobial effects on raw chicken, apple juice, milk, and mixed vegetables, effectively reducing bacterial and fungal populations [137]. Rafati et al. reported the inhibitory effects of nanoemulsions containing the essential oil of Salvia officinalis on the growth of *S. pneumonia* and *P. aeruginosa*, both in the gas and liquid phase [121]. Figure 2 illustrates the diverse antimicrobial characteristics of the referenced nanoparticles.

**Table 4** Summary of select studies conducted in the field of transporting essential oils by nanoparticle

| Formulation | Effective Combination | Microorganism | References |
|---|---|---|---|
| PLGA nanoparticles | Cinnamaldehyde and Eugenol | *Salmonella spp.*; *Listeria spp.* | [183] |
| PLGA nanoparticles | Carvacrol | *Staphylococcus epidermidis* biofilms | [184] |
| Methyl and Ethylcellulose nanoparticles | Thymol | *Staphylococcus aureus*; *Escherichia coli*; *Pseudomonas aeruginosa* | [185] |
| Liposomes | *Origanum dictamnus* essential oil | Gram-positive and gram-negative bacteria, and fungi | [186] |
| PC, PC/PS, PC/SA, PG/CL liposomes | Linalyl acetate, menthol and thymol | *Staphylococcus aureus*; *Escherichia coli* | [187] |
| Nanoemulsion | Eucalyptus | *Proteus mirabilis* | [188] |
| Microemulsion | Ocimum | *Propionibacterium acnes* | [189] |
| Nanoemulsion | Carvacrol, limonene, cinnamaldehyde, and sunflower oil | *Escherichia coli*; *Lactobacillus delbrueckii*; *Saccharomyces cerevisiae* | [190] |
| Nanoemulsion | *Salvia officinalis* Essential Oil | *Haemophilus influenza; Moraxella catarrhalis; Pseudomonas aeruginosa; Streptococcus pneumonia* | [121] |

*PLGA* poly (Lactide-co-glycolic acid), *PC* phosphatidylcholine, *PS* phosphatidylserine, *SA* sphingomyelin, *CL* cardiolipin

## Photothermal and Photodynamic Effects of NPs

The rapidly evolving field of antimicrobial nanomaterials has expanded beyond traditional metal NPs, exploring a diverse array of nanomaterials with promising antibacterial properties. These advanced materials leverage unique surface characteristics and photothermal (PT) and photodynamic (PD) effects to effectively combat bacterial infections. Among these, functionalized polymeric nanoparticles and two-dimensional (2D) nanomaterials such as graphene and MXenes have emerged as particularly potent candidates.

### Functionalized Polymeric Nanoparticles

Functionalized polymeric nanoparticles offer a versatile platform for antibacterial applications. Recent studies have demonstrated their efficacy in delivering antimicrobial agents with enhanced precision and effectiveness. For instance, a novel polymeric nanocarrier system has been developed that exhibits superior antibiofilm activity against multidrug-resistant bacteria [138]. This system's success is attributed to its ability to penetrate biofilms and release antibiotics in a controlled manner, significantly improving treatment outcomes.

### Two-Dimensional (2D) Nanomaterials

The field of 2D nanomaterials has witnessed remarkable advancements, particularly in the application of graphene and MXenes for antibacterial purposes. Graphene-based materials have shown exceptional antibacterial activity due to their unique physicochemical properties. Recent investigations have revealed that graphene oxide nanocomposites can effectively inhibit bacterial growth through multiple mechanisms, including membrane disruption and oxidative stress induction [139]. Furthermore, the incorporation of graphene into wound dressings has demonstrated accelerated healing and infection prevention in vivo [140].

### Graphene-based Nanomaterials

Graphene and its derivatives, such as graphene oxide (GO) and reduced graphene oxide (rGO), have demonstrated remarkable antibacterial activity through multiple mechanisms. Gao et al. (2022) developed a hybrid material combining graphene oxide with a temperature-responsive polymer, demonstrating on-demand antibacterial activity triggered by near-infrared irradiation. This approach allows for spatiotemporal control of antibacterial action, potentially reducing the risk of developing bacterial resistance [141]. Graphene-based materials exhibit excellent photothermal

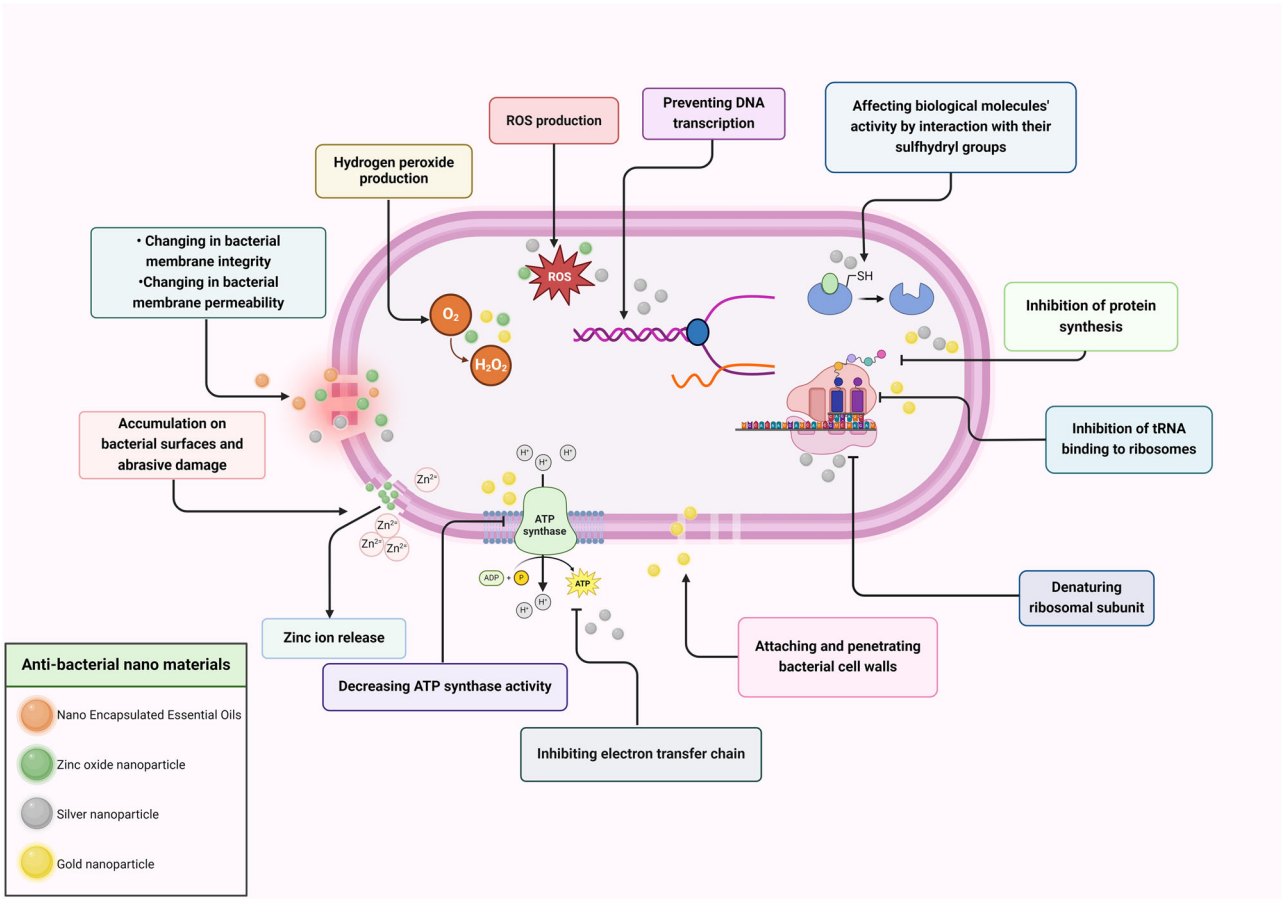


**Fig. 2** Multifaceted mechanisms underlying the intrinsic antimicrobial activities of diverse NPs. This figure depicts the diverse NPs that possess inherent antimicrobial properties, including metal-based nanomaterials (e.g., zinc oxide, silver, gold) and nano-encapsulated essential oils. These NPs exert their microbicidal effects through a variety of mechanisms, which are detailed in the main text. The illustration was created using BioRender.com

conversion efficiency, enabling their use in photothermal therapy (PTT) for localized antibacterial treatment. Additionally, these materials can be functionalized with photosensitizers for photodynamic therapy (PDT). Li et al. developed a multifunctional graphene-based nanocomposite that combined PTT and PDT, demonstrating synergistic antibacterial effects under near-infrared irradiation [142]. A comprehensive study by Shen et al. elucidated the structure-activity relationships of various graphene-based materials, highlighting the importance of surface functionalization in enhancing antibacterial efficacy while minimizing cytotoxicity to mammalian cells [143].

## MXenes

MXenes, a class of 2D transition metal carbides and nitrides, have attracted considerable interest for their antibacterial properties. A pioneering study introduced a MXene-based nanocomposite exhibiting remarkable broad-spectrum antibacterial activity [144]. This material demonstrated a synergistic effect involving physical disruption of bacterial membranes and photothermal antibacterial action, offering a multifaceted strategy for combatting bacterial infections. The photothermal and photodynamic effects of these nanomaterials have been extensively investigated for their potential in antibacterial therapy. A novel graphene-based nanoplatforms showcased exceptional photothermal conversion efficiency and sustained antibacterial effects under near-infrared irradiation [145]. Likewise, an MXene-based photodynamic therapeutic agent displayed enhanced generation of reactive oxygen species and subsequent eradication of bacteria upon light activation [146]. Furthermore, surface functionalization of these nanomaterials has proven essential in enhancing their antibacterial efficacy and biocompatibility. A study on surface-modified graphene quantum dots highlighted their ability to selectively target and eliminate bacteria while exerting minimal cytotoxicity toward mammalian cells [147]. This targeted approach is crucial in the development of safe and efficient antibacterial treatments. The integration of these advanced nanomaterials into practical applications has yielded promising outcomes. For instance, graphene-incorporated surgical

sutures exhibited superior antibacterial properties and enhanced wound healing in animal models [141]. Moreover, MXene-based coatings on medical implants demonstrated prolonged antibacterial effects, potentially reducing the incidence of implant-associated infections [148]. As research advances in this field, attention is increasingly directed towards understanding the long-term implications and potential risks associated with these nanomaterials. A comprehensive investigation into the environmental impact and biodegradability of graphene-based antibacterial materials provided valuable insights into their life cycle and possible ecological consequences [149]. Similarly, studies exploring the biocompatibility and in vivo behavior of MXene-based antibacterial agents have paved the way for their potential clinical application [150].

## Biocompatibility of Antimicrobial NPs

The concept of biocompatibility, which refers to the ability of a substance to interact favorably with the body, has gained attention in the medical field since the mid-20th century [151]. It encompasses the substance's ability to perform its intended function without causing harmful reactions, and its suitability may vary among individuals. Biocompatibility is crucial in the context of drug delivery and the acceptable use of biological substances in specific biological environments [152]. Achieving a high degree of biocompatibility involves avoiding toxic, immunogenic, thrombogenic, and carcinogenic responses within the body [152–154]. Factors such as anatomical variations and the intrinsic properties of biological materials influence biocompatibility [152–154]. Furthermore, the assessment of biocompatibility requires a specific and practical approach due to a limited understanding of biological processes and current methodologies [155]. Therefore, a thorough evaluation of the biocompatibility of nanomaterials is essential before their use in various applications, including medicine. By understanding the potential effects of nanomaterials on organs, tissues, and cells, we can ensure their safe and beneficial utilization in fields such as drug delivery, gene transfer, biosensors, and wound infection treatment, considering different routes of exposure and employing in vitro and in vivo testing methods for toxicity assessment and understanding the mechanisms of action [156–158].

This study comprehensively reviews various NP-based strategies for combating bacterial infections, presenting promising alternatives to conventional antibiotics. However, it is important to acknowledge several limitations within this review. The rapidly evolving nature of nanotechnology research means that some recent developments may not have been fully captured. The heterogeneity among studies makes direct comparisons challenging, particularly with many focusing primarily on in vitro results; thus, translation to in vivo settings and clinical applications necessitates further investigation. The long-term impacts of nanoparticle-based antimicrobials on human health and the environment remain incompletely understood. While these approaches may offer advantages in overcoming existing resistance mechanisms, the potential for bacteria to develop resistance to these new strategies cannot be overlooked. Furthermore, the economic feasibility of large-scale production and implementation compared to conventional antibiotics has not been extensively addressed. Regulatory challenges and variability in biocompatibility also warrant further exploration. These limitations underscore the necessity for ongoing research, especially regarding long-term safety, in vivo efficacy, and the potential for resistance development. Despite these challenges, the diverse range of nanoparticle-based approaches reviewed in this study provides optimism for developing novel and effective strategies to combat bacterial infections. This could potentially revolutionize infection control and enhance healthcare outcomes for future generations.

## Current Challenges and Future Perspectives

The field of NPs-based antimicrobial strategies presents both exciting opportunities and significant challenges. As research progresses, several key areas emerge as critical for the future development and implementation of these innovative approaches. One of the primary challenges lies in translating promising in vitro results to effective in vivo applications. The complex biological environment within living organisms can significantly alter the behavior and efficacy of nanoparticles. Future research must focus on bridging this gap by developing more accurate models that better mimic real-world conditions and conducting comprehensive in vivo studies to validate the efficacy and safety of these nanoparticle-based antimicrobials [159].

Another crucial area for future investigation is the long-term impact of NPs on human health and the environment. While many studies have demonstrated the short-term efficacy of various nanoparticle systems, their long-term effects remain largely unknown. Extended studies are necessary to assess potential accumulation in tissues, interactions with the human microbiome, and environmental persistence. Developing biodegradable nanoparticles or systems that can be safely eliminated from the body will be key to addressing these concerns [160, 161]. The potential for bacteria to develop resistance to NP-based antimicrobials is an important consideration that warrants further exploration. While these novel approaches may initially overcome existing resistance mechanisms, it is crucial to investigate the possibility of new resistance

pathways emerging. Future research should focus on understanding and mitigating potential resistance mechanisms, possibly through the development of multi-modal NP systems that target multiple bacterial vulnerabilities simultaneously [162]. Scaling up the production of NP-based antimicrobials for clinical use presents another significant challenge. Many current synthesis methods are complex and costly, potentially limiting widespread adoption. Future efforts should focus on developing more efficient, cost-effective production methods that maintain consistent quality and efficacy. This may involve exploring new materials, optimizing synthesis processes, or developing innovative manufacturing techniques.

Regulatory challenges pose another hurdle in the path to clinical implementation. The unique properties of NPs often fall outside traditional regulatory frameworks, necessitating the development of new guidelines and standards. Collaboration between researchers, industry, and regulatory bodies will be crucial in establishing appropriate safety and efficacy standards for these novel antimicrobial approaches. Enhancing the specificity and targeting capabilities of NP-based systems represents an important direction for future research. Developing NPs that can selectively target pathogenic bacteria while sparing beneficial microbiota could significantly reduce side effects and improve treatment outcomes. This may involve exploring novel targeting ligands, responsive nanoparticle systems, or bacteria-specific delivery mechanisms. The integration of NP-based antimicrobials with other emerging technologies, such as CRISPR-Cas systems or artificial intelligence-driven drug discovery, offers exciting possibilities for future advancements. These synergistic approaches could lead to more personalized and effective treatment strategies. Lastly, as the field advances, there is a growing need for standardized testing and characterization methods to ensure consistency and comparability across different studies and nanoparticle systems. Establishing these standards will be crucial for the reliable evaluation and eventual clinical translation of NP-based.

## Conclusion

This study provides a comprehensive review of NP-based strategies for combating bacterial infections, presenting promising alternatives to traditional antibiotics. Key findings highlight the enhanced drug delivery capabilities of liposomal systems, particularly for hydrophobic antimicrobials, which offer improved targeting and prolonged circulation times. Polymeric micelles have demonstrated efficacy in delivering hydrophobic drugs, with specific polymer-drug combinations showing synergistic effects against diverse pathogens. SLNs have emerged as versatile carriers suitable for both topical and oral antimicrobial applications, offering enhanced drug stability and bioavailability. Dendrimers, especially those functionalized with silver or quaternary ammonium salts, exhibit potent antimicrobial activity through multiple mechanisms. Metal NPs, notably ZnONPs and silver, possess inherent antimicrobial properties and can augment the efficacy of conventional antibiotics. Gold NPs serve as effective carriers for antimicrobial agents. Nano-encapsulated essential oils show promise in overcoming the limitations of free essential oils by providing improved stability and controlled release of antimicrobial compounds. As the research in NP-based antimicrobial strategies continues to advance, addressing the highlighted challenges and focusing on future perspectives will be essential for translating these promising findings into effective clinical applications.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare no competing interests.

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