



Review

Advanced Nanoparticles in Combating Antibiotic Resistance: Current Innovations and Future Directions

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Abstract: Antibiotic resistance poses a significant global health challenge, undermining the effectiveness of conventional treatments and increasing mortality rates worldwide. Factors such as the overuse and misuse of antibiotics in healthcare and agriculture, along with poor infection control practices, have accelerated the emergence of resistant bacterial strains. The stagnation in the development of new antibiotics, compounded by economic and biological challenges, has necessitated alternative approaches to combat resistant infections. Nanotechnology provides a promising solution using nanoparticles (NPs), which combat bacteria through mechanisms like membrane disruption and reactive oxygen species (ROS) generation. Metal-based nanoparticles such as silver and zinc oxide possess intrinsic antimicrobial properties, while polymer- and carbon-based nanoparticles enhance drug delivery and biofilm penetration. Unlike conventional antibiotics, nanoparticles operate through multi-mechanistic pathways, reducing the likelihood of resistance development and improving treatment efficacy. This review aims to provide an updated, in-depth look at recent advances in nanoparticle research targeting antibiotic resistance, discussing different types of nanoparticles, mechanisms of action, and current challenges and opportunities. By exploring the evolving role of nanotechnology in addressing this crisis, this review intends to highlight the potential for nanoparticles to transform the treatment landscape for resistant bacterial infections and inspire further research into these innovative solutions.



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1. Introduction

Antibiotic resistance has emerged as one of the most critical threats to global public health, presenting serious implications for modern medicine. As bacteria evolve to withstand commonly used antibiotics, infections that were once easily treatable can now result in severe health complications and increased mortality [1]. According to the WHO and CDC, antibiotic-resistant infections cause hundreds of thousands of deaths each year. If current trends continue, this number could exceed ten million annually by 2050 [2,3]. Several factors drive the development of antibiotic resistance. First, the overuse and misuse of antibiotics in healthcare settings have enabled bacteria to adapt and evolve more rapidly. Prescribing antibiotics for viral infections, such as the common cold, and failure to complete antibiotic courses are examples of human behaviors that promote resistance [4–6]. Additionally, antibiotic use in agriculture, especially in livestock, contributes significantly to resistance. Antibiotics administered to promote animal growth can lead to the emergence of resistant bacterial strains that reach humans through the food chain and environmental runoff [7,8]. Poor infection control practices in healthcare facilities further accelerate

the spread of resistant bacteria among vulnerable populations, such as the elderly and immunocompromised patients [9,10].

Antimicrobial resistance (AMR) poses a critical global health challenge, with recent analyses highlighting its escalating impact. A comprehensive study estimated that in 2021, there were approximately 4.71 million deaths associated with bacterial AMR, including 1.14 million deaths directly attributable to antibiotic-resistant infections. Notably, while deaths among children under five decreased by over 50% from 1990 to 2021, those among adults aged 70 and older increased by more than 80%, underscoring the heightened vulnerability of the aging population. Projections indicate a grim future if effective interventions are not implemented. AMR-related deaths are expected to rise to 1.91 million annually by 2050, a substantial increase from current figures. Cumulatively, over the next three decades, antibiotic-resistant infections could lead to an additional 39 million deaths worldwide [2,11,12]. Antibiotic resistance also threatens essential medical procedures, such as surgeries, cancer treatments, and organ transplants, which rely on effective antibiotics to prevent infections. The increasing threat of resistant infections makes these procedures riskier, potentially limiting their feasibility [2,13].

To address the limitations of traditional antibiotics, researchers are increasingly turning to nanotechnology as a promising alternative. Nanoparticles typically ranging from 1 to 100 nanometers in size, possess unique physical and chemical properties that differentiate them from bulk materials, making them particularly suitable for applications in combating bacterial infections [14,15]. Nanoparticles can be engineered with high surface-area-to-volume ratios, tunable surface chemistries, and diverse mechanisms of action, enabling them to overcome several challenges faced by conventional antibiotics.

To further understand the effectiveness of nanoparticles in combating antibiotic resistance, it is important to consider their performance against specific bacterial species. The minimum inhibitory concentration (MIC) is a crucial measure for determining the lowest concentration of nanoparticles required to inhibit bacterial growth. For instance, nanoparticles such as silver and zinc oxide have demonstrated effective MIC values against common bacterial pathogens such as *Escherichia coli* and *Staphylococcus aureus*. Additionally, in vivo potency studies highlight the ability of these nanoparticles to remain effective in living organisms, providing evidence of their potential for systemic delivery and local treatment. Studies have shown that silver nanoparticles exhibit high efficacy in treating infections caused by multidrug-resistant bacteria, with their in vivo efficacy being validated in animal models of wound infection [16].

Nanoparticles exhibit a range of properties that make them versatile tools against resistant bacteria. For example, metal-based nanoparticles, such as silver (AgNPs) and zinc oxide (ZnO NPs), exhibit intrinsic antibacterial properties by disrupting bacterial cell membranes and generating ROS that damage bacterial deoxyribonucleic acid (DNA) and proteins, leading to cell death [17–19]. Despite these promising properties, nanoparticles also have limitations, including potential toxicity, challenges with large-scale production, and difficulty in ensuring consistent quality and stability. The long-term effects of nanoparticle accumulation in the body are not fully understood, and concerns about their environmental impact remain. Additionally, the biodistribution of nanoparticles can be unpredictable, and their clearance from the body is not always efficient, which could lead to unintended side effects. However, despite these challenges, nanoparticles have shown considerable promise in medical applications. For example, liposomal formulations like Doxil are currently used for chemotherapy, silver nanoparticles in wound healing, and iron oxide nanoparticles in MRI imaging and targeted drug delivery [20,21].

Nanoparticles can act as drug carriers to improve the targeted delivery of antibiotics, significantly enhancing their ability to penetrate bacterial biofilms and effectively reach

infection sites. Recent studies have demonstrated that nanoparticles, including liposomal nanoparticles, polymeric micelles, and metal-based nanoparticles, offer superior biofilm penetration compared to conventional antibiotics. For example, research has shown that silver nanoparticles functionalized with antibiotics can disrupt biofilm formation and enhance bacterial susceptibility to treatment, particularly against resistant strains like *Pseudomonas aeruginosa* and *Staphylococcus aureus*. These nanoparticles, due to their small size and customizable surface properties, enable enhanced antibiotic delivery directly to the infection site while overcoming barriers like biofilm resistance. By encapsulating drugs, nanoparticles provide sustained and controlled release, reducing systemic toxicity and improving treatment outcomes in chronic infections caused by multidrug-resistant pathogens [22–24]. This targeted delivery minimizes systemic side effects and increases the local concentration of antibiotics at the infection site, enhancing treatment efficacy. Unlike conventional antibiotics, many nanoparticles do not rely on specific bacterial receptors, allowing them to bypass common resistance mechanisms. Their physical interactions with bacterial membranes or release of toxic ions (e.g., silver ions) can disrupt bacterial cells without relying on traditional biochemical pathways. Nanoparticles, such as AgNPs, interact with bacterial cell membranes through electrostatic attraction or van der Waals forces, which enable the nanoparticles to attach to the bacterial surface. Once attached, AgNPs can penetrate the bacterial cell membrane and cause structural damage. This leads to the formation of pores or holes in the membrane, resulting in increased membrane permeability and leakage of essential intracellular contents, ultimately causing bacterial cell death [25–27].

The unique mechanisms of nanoparticles offer several advantages over traditional antibiotics, including a reduced likelihood of resistance development due to their multi-mechanistic approach, making it more difficult for bacteria to develop resistance [15,28]. Additionally, nanoparticles enable targeted delivery, allowing for reduced antibiotic doses while maintaining therapeutic efficacy. This can help reduce side effects and decrease the selective pressure on bacteria to develop resistance [18]. Despite the urgent need for new antibiotics, the discovery and development of novel antibacterial agents have slowed significantly. Developing antibiotics is time-consuming and costly, with relatively few novel agents reaching the market in recent decades. This stagnation is exacerbated by bacteria's rapid adaptability and the limited innovation in drug pipelines. New antibiotics must often outperform the rapidly evolving defenses of resistant bacteria. Broad-spectrum antibiotics, while effective against various bacteria, can harm beneficial microbiota, leading to potential adverse effects and increased susceptibility to secondary infections. Economic disincentives also hinder antibiotic development, as antibiotics are typically prescribed for short courses, unlike chronic disease medications, which provide a more sustainable revenue model for pharmaceutical companies. Moreover, antibiotic resistance reduces the effective lifespan of each antibiotic, further diminishing financial incentives for research and development [2,13,29].

While nanoparticles have emerged as a promising solution due to their unique properties and mechanisms of action, they are not the only approach being explored. Several other innovative strategies are currently being investigated to tackle antibiotic-resistant infections. Thin-film coatings, for example, are being developed for medical devices and surfaces to prevent bacterial colonization and biofilm formation. These coatings can be designed to release antimicrobial agents or use materials with inherent antimicrobial properties, thereby reducing the risk of infection in healthcare settings. Similarly, antimicrobial peptides are gaining attention for their ability to disrupt bacterial cell membranes, providing a potential alternative to traditional antibiotics. These naturally occurring molecules have shown effi-

cacy against multidrug-resistant bacteria and offer a different mode of action that reduces the likelihood of resistance development [30,31].

Small molecules, including enzyme inhibitors and compounds that block bacterial communication systems (such as quorum sensing inhibitors), represent another promising avenue of research. These molecules can either enhance the activity of existing antibiotics or directly target resistance mechanisms in bacteria. Additionally, biomimetic polymers that mimic natural antimicrobial substances are being developed as part of a broader strategy to combat bacterial resistance. These polymers can be engineered to selectively interact with bacterial cells, offering targeted antimicrobial activity while minimizing toxicity to human cells [32,33].

Given the pressing nature of antibiotic resistance and the promising applications of nanoparticles, understanding and developing nanoparticle-based approaches to treat resistant infections is increasingly crucial. This review aims to provide an updated, in-depth look at recent advances in nanoparticle research targeting antibiotic resistance, discussing different types of nanoparticles, mechanisms of action, and current challenges and opportunities. By exploring the evolving role of nanotechnology in addressing this crisis, this review intends to highlight the potential for nanoparticles to transform the treatment landscape for resistant bacterial infections and inspire further research into these innovative solutions.

2. Types of Nanoparticles Used Against Antibiotic-Resistant Bacteria

Nanoparticles come in various forms and are extensively utilized in healthcare and medicine, particularly in antimicrobial chemotherapy. Metal-based nanoparticles stand out for their versatility, finding applications not only in medicine and biotechnology but also in electronics and materials science. Their unique physical and chemical properties, attributed to their nanoscale size and high surface-area-to-volume ratio, make them highly effective in diverse contexts. The following sections delve into metal-based nanoparticles, exploring their synthesis methods, applications, benefits, and challenges [34].

2.1. Metal and Metal Oxide Nanoparticles

Metal and metal oxide NPs are nanoscale structures primarily composed of metal atoms or metal compounds, typically measuring between 1 and 100 nanometers (nm). At this scale, they exhibit unique physical and chemical properties that set them apart from their bulk counterparts. These characteristics enable them to perform specialized functions, including antimicrobial activity, which is achieved through distinct mechanisms depending on the material. Metal-based nanoparticles such as silver (Ag), gold (Au), zinc (Zn), and copper (Cu), along with metal oxides like zinc oxide (ZnO), are among the most extensively researched and utilized in antimicrobial nanotechnology. These nanoparticles each demonstrate unique properties and mechanisms of action, offering versatile solutions for combating bacterial infections and other microbial threats [26,35,36].

In addition to standalone nanoparticles, metal-based thin-film coatings are gaining prominence as an antimicrobial strategy. These coatings are applied to surfaces in medical devices, wound dressings, and other healthcare-related materials. Thin-film coatings made from metals like silver and copper are known to release metal ions over time, providing continuous antimicrobial action. The ability of these coatings to prevent bacterial colonization and biofilm formation is particularly important for reducing hospital-acquired infections and improving the longevity of medical devices. The development and application of thin-film coatings are a crucial area of research in the battle against resistant bacterial infections [30,37].

Silver-based nanoparticles are among the most widely studied metal nanoparticles due to their potent antimicrobial properties. These nanoparticles can be synthesized using various methods, such as chemical reduction, physical vapor deposition, and biological methods. One of the key advantages of silver nanoparticles is the ability to precisely control their size and shape during synthesis, which allows tailoring their properties for specific applications, such as providing broad-spectrum antimicrobial activity. This versatility in synthesis contributes to their effectiveness in diverse applications, including wound dressings, antimicrobial coatings, and water purification systems.

The primary antimicrobial mechanism of AgNPs involves the release of silver ions (Ag^+), which are central to their bactericidal action. These ions disrupt microbial cellular processes by interacting with bacterial cell membranes, causing damage to their structure and increasing membrane permeability. This leads to leakage of essential intracellular contents and eventual cell death. Additionally, silver ions deactivate enzymes within the microbial cells and inhibit crucial processes like DNA and ribonucleic acid (RNA) synthesis, further impairing the bacteria's ability to function and replicate. The dual mechanisms of ion release and membrane disruption make silver nanoparticles highly effective against a broad range of pathogens. Furthermore, silver nanoparticles are renowned for their exceptional electrical and thermal conductivity, which enhances their antimicrobial properties. The combination of ion release, physical disruption, and unique material properties gives AgNPs a significant advantage over conventional antimicrobial agents, as they are less likely to induce resistance in bacteria. These properties make silver nanoparticles an ideal candidate for a variety of applications, particularly in medical settings where their ability to prevent infection and promote healing is of great value [38–41].

Gold nanoparticles (AuNPs) are widely studied for their potential in various biomedical applications, including antimicrobial therapy. They are synthesized using methods such as chemical reduction, seed-mediated growth, and green synthesis approaches that utilize plant extracts or other biological agents. While gold nanoparticles themselves exhibit relatively weak intrinsic antimicrobial activity compared to silver, their primary strength lies in their ability to act as effective carriers for antimicrobial agents. By functionalizing AuNPs with antibiotics, antimicrobial peptides, or other bioactive molecules, their delivery and efficacy against resistant bacteria can be significantly enhanced.

The antimicrobial mechanism of AuNPs primarily involves their interaction with bacterial cell membranes. AuNPs attach to the microbial cell surface, where their size, shape, and surface chemistry play a crucial role in disrupting the integrity of the cell membrane. This disruption increases membrane permeability, which allows the entry of the loaded antimicrobial agents, facilitating their action inside the bacterial cells. Although AuNPs do not exhibit the same intrinsic bactericidal properties as silver nanoparticles, their ability to enhance the effect of other antimicrobial agents through this membrane disruption mechanism makes them highly effective in combatting resistant microbial strains. In addition to their antimicrobial activity, gold nanoparticles are known for their unique optical, electrical, and thermal properties, which further contribute to their versatility in biomedical applications. These properties make AuNPs ideal for use in diagnostic imaging, photothermal therapy, and targeted drug delivery. Moreover, their biocompatibility and non-toxic nature have led to their increasing use in antimicrobial coatings and the development of therapeutic nanomaterials aimed at combating resistant infections. The size, shape, and surface chemistry of AuNPs can be meticulously tailored during synthesis, optimizing their functionality for specific medical applications [36,42,43].

Zinc-based nanoparticles are increasingly recognized for their antimicrobial properties and wide range of applications. These nanoparticles are typically synthesized using methods such as the sol–gel process, chemical precipitation, and environmentally friendly

green synthesis techniques that utilize plant extracts. Their antimicrobial activity is largely attributed to the generation of ROS when they interact with microbial cells. These ROS, including hydroxyl radicals and hydrogen peroxide, induce oxidative stress in bacterial cells, leading to damage of cellular membranes, proteins, and DNA. This oxidative damage ultimately results in bacterial cell death.

ZnNPs are widely used in various protective coatings due to their dual benefits: they provide corrosion resistance while also offering antimicrobial protection. Their effectiveness is particularly valuable in medical, industrial, and agricultural settings. In addition to coatings, zinc nanoparticles are commonly employed in sunscreens and cosmetics because of their effective ultraviolet blocking capabilities combined with antimicrobial effects. These properties make ZnNPs highly versatile, as they are also incorporated into paints to reduce microbial contamination in various surfaces. Moreover, zinc nanoparticles have found applications in agriculture, where they are added to pesticides and fertilizers to minimize microbial contamination. Their ability to prevent the growth of harmful bacteria while being safe for human skin and the environment further enhances their utility. The combined benefits of strong antimicrobial activity, UV protection, and minimal toxicity make ZnNPs an invaluable resource in a broad spectrum of industries [44–46].

Copper-based nanoparticles are widely recognized for their potent antimicrobial properties and are synthesized using techniques such as electrochemical methods, thermal decomposition, and chemical reduction. These nanoparticles exhibit antimicrobial activity primarily through the release of copper ions (Cu^{2+}), which disrupt microbial cell membranes and inhibit vital enzymatic functions. The copper ions interact with bacterial cell membranes, increasing their permeability, which leads to the leakage of cellular contents and ultimately bacterial cell death. Furthermore, copper ions can bind to and inactivate bacterial enzymes, disrupting metabolic processes and inhibiting bacterial growth. CuNPs are utilized extensively in the food packaging industry and as antimicrobial surface coatings for high-touch areas, effectively reducing microbial contamination. Their antimicrobial properties make them particularly suitable for applications in textiles, coatings, and medical devices, where they help inhibit bacterial and microbial growth. The effectiveness of CuNPs depends on various factors, including the size, shape, concentration, and stabilizing agents used in their synthesis. Research is ongoing to enhance their efficiency, minimize toxicity, and expand their potential applications across multiple industries [47–49].

Zinc oxide-based antimicrobial NPs (ZnO NPs) are nanoscale particles composed of zinc and oxygen atoms, typically ranging from 1 to 100 nanometers in size. This compound consists of zinc cations (Zn^{2+}) and oxide anions (O^{2-}). At the nanoscale, ZnO nanoparticles possess unique properties that differ significantly from their bulk form, making them highly valuable for diverse applications. Their antimicrobial activity is primarily linked to the generation of ROS, which induce oxidative stress in microbial cells. ZnO NPs are widely used in sunscreens and cosmetics due to their effective UV-blocking capabilities combined with antimicrobial effects. Known for their high biocompatibility, they are widely studied for medical and pharmaceutical applications, such as tissue engineering and drug delivery. Additionally, ZnO nanoparticles function as photocatalysts under light exposure, making them highly effective in water and air purification by facilitating the breakdown of organic pollutants [50,51].

Iron oxide-based nanoparticles (FeNPs), primarily composed of iron (Fe) and oxygen, form compounds like magnetite (Fe_3O_4), hematite (Fe_2O_3), and maghemite ($\gamma\text{-Fe}_2\text{O}_3$). These nanoparticles are widely used in biomedical applications, particularly for targeted drug delivery, and exhibit antimicrobial properties when coated or functionalized with antimicrobial agents. Magnetite and maghemite nanoparticles, known for their strong magnetic characteristics, are especially valuable in magnetic-based technologies, including MRI

contrast agents, magnetic drug delivery systems, and magnetic hyperthermia for cancer therapy. The antimicrobial mechanism of FeNPs is primarily based on the release of iron ions (Fe^{2+} or Fe^{3+}) and the generation of ROS upon contact with bacterial cells. These ROS, including hydroxyl radicals and superoxide ions, induce oxidative stress in microbial cells, leading to the degradation of cell membranes, proteins, and DNA. The oxidative damage caused by ROS results in cell death. In addition, iron oxide nanoparticles can interact with bacterial cell membranes, disrupting their integrity and increasing permeability, further contributing to their antimicrobial action.

FeNPs have demonstrated broad-spectrum antimicrobial activity, proving effective against various Gram-positive and Gram-negative bacteria, as well as fungal species. Their versatility makes them valuable for a wide range of applications, from biomedical to environmental settings. In nanomedicine, these nanoparticles are widely used for targeted drug delivery, cell labeling, and high-precision imaging techniques. When functionalized with biocompatible materials or specific ligands, they enable advanced applications such as targeted therapeutic interventions, improving the efficiency of drug delivery and reducing systemic toxicity [26,52,53].

Titanium dioxide-based antimicrobial NPs (TiO_2 NPs) are widely utilized for their antimicrobial properties, which are significantly enhanced when combined with UV light. Upon UV irradiation, these nanoparticles exhibit strong photocatalytic activity, producing ROS such as superoxide ions and hydroxyl radicals. These ROS possess potent oxidative properties that can damage microbial cell membranes, proteins, and DNA, ultimately leading to the inactivation and death of microorganisms. TiO_2 NPs demonstrate broad-spectrum antimicrobial activity, making them effective against bacteria, viruses, and fungi, and are therefore valuable for disinfection and sterilization applications. Beyond their antimicrobial uses, titanium dioxide nanoparticles are commonly incorporated into sunscreens and other sun protection products as physical UV blockers due to their ability to absorb and scatter UV radiation. Additionally, their unique surface properties make them effective catalysts in chemical reactions, with applications in organic synthesis and environmental remediation, including the degradation of pollutants in water and air purification processes [54,55].

2.2. Lipid-Based Nanoparticles

Lipid-based nanoparticles are nanoscale carriers primarily composed of lipids, which are biocompatible and biodegradable molecules. These nanoparticles have gained significant attention in antimicrobial applications due to their ability to encapsulate and deliver antimicrobial agents effectively. Their unique properties, including controlled drug release, enhanced cellular uptake, and low toxicity, make them suitable for combating bacterial infections, including those caused by antibiotic-resistant strains [56].

Liposomal nanoparticle-based antimicrobial NPs are lipid-based carriers engineered to deliver antimicrobial agents effectively. These nanoparticles consist of phospholipid bilayers surrounding an aqueous core, enabling them to encapsulate both hydrophilic and hydrophobic antimicrobial agents. Liposomal antimicrobial nanoparticles protect encapsulated drugs from degradation, enhance their bioavailability, and allow for controlled and targeted drug release. The primary advantage of liposomal nanoparticles is their ability to deliver antibiotics and other antimicrobials directly to infection sites, improving efficacy while minimizing systemic toxicity. They are particularly effective against biofilms, as their structure enables penetration into these protective bacterial layers. Liposomal antimicrobial NPs have been utilized to deliver drugs like vancomycin, colistin, and amphotericin B for treating resistant bacterial and fungal infections. Their biocompatibility, versatility, and ability to overcome resistance mechanisms make them a promising tool in combating antimicrobial resistance [57,58]. Solid lipid nanoparticles (SLNs) and nanostructured lipid

carriers (NLCs) are two such nanoparticle systems that have shown potential in drug delivery, providing controlled release and enhancing the bioavailability of antimicrobial agents.

In addition to nanoparticles, antimicrobial polymers have also garnered attention for their ability to directly target and neutralize microorganisms. Soluble antimicrobial polymers, such as polyhexamethylene biguanide and chitosan, are commonly used in various formulations for their antimicrobial activity when dissolved in solution. These polymers exhibit effective antimicrobial properties by interacting with the microbial cell membranes and disrupting their integrity. However, their application can be limited by solubility issues, degradation rates, and the potential for leaching, which may lead to reduced efficacy over time. On the other hand, antimicrobial polymers incorporated into nanoparticles offer enhanced stability, controlled release, and more effective targeted delivery. When embedded in nanoparticles, these polymers are shielded from premature degradation, ensuring prolonged antimicrobial activity. Additionally, nanoparticles provide the advantage of facilitating better penetration into bacterial biofilms, which is often a barrier in chronic infections. Nanoparticle-based systems also minimize systemic toxicity and improve the bioavailability of antimicrobial agents, making them suitable for a wide range of medical applications. Both forms of antimicrobial polymers—soluble and nanoparticle-bound—have distinct benefits and can be chosen based on the specific needs of the therapeutic application. Soluble polymers are ideal for applications that require immediate release, while nanoparticle-bound polymers are better suited for sustained release and targeted treatment strategies [17,59,60].

Solid lipid nanoparticles are submicron-sized carriers composed of a solid lipid core stabilized by surfactants. These nanoparticles are designed to encapsulate and deliver antimicrobial agents, offering protection from degradation and controlled drug release. SLNs are synthesized using methods such as high-pressure homogenization, microemulsion techniques, and solvent evaporation, which allow precise control over particle size and drug-loading efficiency. SLNs exhibit high biocompatibility and stability, making them ideal for encapsulating hydrophobic antibiotics and antifungal agents. Their solid lipid matrix enables sustained release of antimicrobial agents, ensuring prolonged therapeutic activity. Furthermore, SLNs can penetrate bacterial biofilms and target infection sites effectively.

SLNs differ from traditional micelle structures, which are typically formed by surfactants in aqueous solutions and lack the solid lipid core. In contrast, SLNs offer a more stable and controlled drug release profile compared to micelles, which are less durable and may lack the capacity for prolonged release. SLNs are also more effective in encapsulating hydrophobic drugs, whereas micelles are primarily used for solubilizing poorly water-soluble drugs. The lipid composition of SLNs typically involves a single solid lipid like stearic acid, palmitic acid, and glyceryl monostearate, and they are stabilized using surfactants such as Poloxamer 188 or Tween 80. This simple composition provides a stable platform for drug delivery, but it may have limitations in terms of drug loading capacity compared to nanostructured lipid carriers. SLNs are primarily used in the treatment of resistant bacterial infections, fungal diseases, and wound healing, where localized and controlled drug delivery is essential. Their advantages, such as reduced systemic toxicity, scalability, and enhanced bioavailability, make SLNs a promising platform in the development of antimicrobial therapies [61–63].

Nanostructured lipid carriers are advanced lipid-based nanoparticles composed of a mixture of solid and liquid lipids, stabilized by surfactants. This hybrid structure provides greater drug-loading capacity and improved stability compared to Solid Lipid Nanoparticles (SLNs), which are composed only of solid lipids. NLCs are synthesized using methods like high-pressure homogenization, ultrasonication, and solvent emulsification techniques,

allowing for precise control over particle size and drug encapsulation. The hybrid lipid composition of NLCs offers flexibility in drug loading, particularly for poorly water-soluble agents. Unlike traditional micelles, which are typically composed of surfactants in aqueous solutions, NLCs contain a solid lipid matrix in combination with liquid lipids, offering a more stable and controlled drug release profile. Micelles, while useful for solubilizing hydrophobic drugs in aqueous environments, lack the solid matrix and often show less stability over time compared to NLCs.

NLCs are effective carriers for antimicrobial agents, enhancing the solubility, stability, and bioavailability of poorly water-soluble drugs. Their ability to encapsulate antibiotics, antimicrobial peptides, or bioactive compounds protects these agents from degradation and ensures controlled and sustained release. This prolonged drug activity improves treatment efficacy against bacterial infections, including those caused by multidrug-resistant strains. The unique structure of NLCs also enables them to penetrate bacterial biofilms, a common barrier in chronic infections, making them particularly valuable in treating difficult-to-treat infections. The formation of NLCs requires a careful balance of solid and liquid lipids, which contributes to their unique properties. NLCs typically consist of a combination of solid lipids like stearic acid or palmitic acid and liquid lipids such as Capryol 90 or oleic acid. The ratio of solid to liquid lipids is crucial for the successful formation of NLCs, with common ratios ranging from 1:1 to 3:1, depending on the desired characteristics of the nanoparticles. This lipid composition provides enhanced drug-loading capacity compared to SLNs, which use only solid lipids. Additionally, the incorporation of liquid lipids in NLCs can help improve the release profile of encapsulated drugs, making NLCs a versatile platform for controlled drug delivery. NLC-based formulations have shown promise in treating skin infections, respiratory infections, and wound healing, offering a potent alternative to conventional antibiotic therapies. Their biocompatibility, tunable release profiles, and ability to encapsulate a wide range of antimicrobial agents make them suitable for systemic, topical, and localized drug delivery applications [64–66].

2.3. Polymer-Based Nanoparticles

Polymer-based nanoparticles are nanoscale structures made primarily from polymers, which are large molecules composed of repeating monomer units. Typically measuring tens to hundreds of nanometers, these nanoparticles are highly adaptable and have applications in various fields. They can be synthesized using either natural or synthetic polymers. Common synthetic polymers include polyethylene, polyvinyl chloride (PVC), and polystyrene, while natural polymers such as chitosan, alginate, and cellulose are frequently utilized in nanoparticle formulations [67].

Polymer-based nanoparticles have garnered significant attention for their potential in diverse applications, particularly in drug delivery, imaging, and as carriers for bioactive agents. Their adaptability has made them valuable in biotechnological applications such as DNA and RNA delivery, protein purification, and cell labeling. These nanoparticles offer unique advantages, including biocompatibility, the ability to encapsulate a wide range of substances, and tailored release profiles, making them essential tools in modern medicine and biotechnology [67–69].

Poly-lactic-co-glycolic acid (PLGA) NPs are biodegradable and biocompatible nanoscale structures composed of glycolic acid and lactic acid copolymers. They are extensively utilized in the medical, pharmaceutical, and biotechnology fields, particularly in drug delivery, tissue engineering, and diagnostics due to their versatile and beneficial properties [69,70].

In drug delivery applications, PLGA nanoparticles slowly degrade into non-toxic byproducts, glycolic acid and lactic acid, which are naturally processed and eliminated by the body. This characteristic makes them particularly effective for encapsulating antibiotics

and other therapeutic agents, protecting them from premature degradation and enabling controlled, sustained release. This controlled release enhances therapeutic efficacy and minimizes side effects.

The characteristics of PLGA nanoparticles, such as shape, size, and drug release kinetics, can be precisely controlled by modifying factors like the molecular weight, lactic acid-to-glycolic acid ratio, and processing methods [71,72]. PLGA nanoparticles play a crucial role in vaccine development, enabling the controlled release of antigens and adjuvants to enhance immune responses and improve vaccine effectiveness. Additionally, they can be loaded with antimicrobial agents, such as antibiotics and antimicrobial peptides, serving as targeted carriers that deliver these agents directly to infection sites for more efficient treatment [72].

Polystyrene NPs are nanoscale particles made from the synthetic polymer polystyrene, which is derived from the monomer styrene. Polystyrene, a thermoplastic polymer, is valued for its high optical clarity and excellent electrical insulation properties. These nanoparticles are versatile and widely used across various fields. When functionalized with antimicrobial surface modifications, they provide localized antimicrobial effects, making them particularly useful in medical applications such as wound dressings, catheters, and surgical implants. In biomedical applications, Polystyrene nanoparticles are employed in imaging, drug delivery, and diagnostics. They can be functionalized with biomolecules for targeted drug delivery or used as carriers for contrast agents in imaging techniques such as MRI and CT scans [17,73].

Polyethylene glycol (PEG) is a biocompatible and water-soluble polymer widely used in nanoparticle formulations for various applications. PEG NPs are especially significant in drug delivery systems, where they encapsulate genes, drugs, or bioactive compounds, protecting them from degradation and allowing for controlled, sustained release [70]. The process of PEGylation, which involves attaching PEG chains, enhances the pharmacokinetics and bio-distribution of therapeutic agents, thereby improving their efficacy. PEG nanoparticles also play a crucial role in tissue engineering and regenerative medicine, where they are incorporated into scaffolds or hydrogels to enable the controlled release of growth factors and cells, supporting tissue regeneration. Their shape, size, and drug release kinetics can be precisely adjusted by modifying the molecular weight of PEG and the nanoparticle formulation, allowing for customization in drug delivery and other biomedical applications [17].

Chitosan nanoparticles are biocompatible and biodegradable nanoscale particles derived from chitosan, a polysaccharide obtained from chitin, which is found in the shells of crustaceans like crabs and shrimp. Due to their unique properties, they have attracted significant interest in biotechnology, pharmaceuticals, and materials science. One of their primary applications is in drug delivery systems, where they encapsulate drugs, genes, or bioactive compounds, enabling controlled and sustained release. This enhances therapeutic efficacy while minimizing side effects. Additionally, chitosan nanoparticles improve drug permeability across biological barriers, such as the blood–brain barrier and gastrointestinal epithelium, increasing bioavailability. Beyond drug delivery, chitosan nanoparticles are widely used in tissue engineering and wound dressings due to their ability to reduce inflammation, promote wound healing, and form a protective barrier against infections. Moreover, chitosan nanoparticles possess intrinsic antimicrobial properties, effectively inhibiting the growth of bacteria, fungi, and certain viruses. Their antimicrobial mechanism involves disrupting microbial cell membranes and interfering with essential cellular processes, making them highly effective for various biomedical applications [70,74].

Polycaprolactone (PCL) is a versatile polymer commonly used in nanoparticle formulations due to its unique properties and adaptability. PCL nanoparticles are widely applied

in drug delivery systems, where they encapsulate drugs, genes, or bioactive compounds, protecting them from degradation while allowing for controlled and sustained release. PCL is especially beneficial for the delivery of hydrophobic drugs, which are often difficult to administer using conventional drug delivery systems [75]. PCL NPs can be engineered to carry antimicrobial agents, including antimicrobial peptides, antibiotics, or other bioactive compounds, either encapsulated within the nanoparticle matrix or adsorbed onto their surface. This enhances their effectiveness against infections. Additionally, the size, shape, and drug release kinetics of PCL nanoparticles can be precisely controlled during synthesis, allowing for customization to meet specific needs such as targeted delivery and optimized release profiles. These adaptable properties make PCL NPs a valuable tool in biomedical and pharmaceutical applications [76,77].

Polyethyleneimine (PEI) NPs are synthetic and highly versatile, known for their unique properties, which make them ideal for various applications, including gene transfection, drug delivery, and antimicrobial treatments. As cationic nanoparticles, PEI can effectively disrupt bacterial cell membranes, contributing to its potent antimicrobial effects. PEI nanoparticles have shown the ability to penetrate and disrupt biofilms, which are structured communities of microorganisms encased in a protective extracellular matrix. Since biofilms are often resistant to antibiotics, PEI nanoparticles provide a valuable tool for overcoming this challenge by breaking down the biofilm's structural integrity and inhibiting the growth of bacteria, fungi, and certain viruses [78,79].

In gene delivery systems, PEI NPs are extensively employed due to their capacity to bind and condense negatively charged nucleic acids (such as DNA or RNA) into nanoparticles, facilitating their entry into cells for effective gene transfection. The cationic charge of PEI enhances interactions with negatively charged cell membranes, promoting efficient cellular uptake. Similarly, in drug delivery applications, PEI nanoparticles can encapsulate therapeutic agents, shielding them from degradation and enabling controlled release. The positive charge of PEI further facilitates targeted delivery to cells, ensuring effective treatment outcomes. These properties make PEI nanoparticles an essential tool in biotechnology, pharmaceuticals, and antimicrobial therapy [79].

2.4. Carbon-Based Nanoparticles

Carbon-based nanoparticles are nanoscale materials primarily composed of carbon atoms, and they are available in various forms, including graphene oxide (GO), fullerenes, carbon nanotubes (CNTs), and graphene quantum dots (GQDs). These nanoparticles have garnered significant attention in recent years due to their exceptional mechanical, electrical, and thermal properties, as well as their versatility in various applications across numerous fields, including medicine, biotechnology, environmental science, and electronics. Among the various types of carbon-based NPs, GO has particularly attracted attention as an antimicrobial agent. GO consists of a single layer of carbon atoms arranged in a hexagonal lattice, with oxygen-containing functional groups such as hydroxyl, carboxyl, and epoxy groups attached to its surface [80]. These functional groups not only make GO hydrophilic and dispersible in aqueous solutions but also enhance its interactions with microbial cells. The antimicrobial activity of GO arises from its ability to physically interact with and damage microbial cell membranes. The high surface area of GO allows for the adsorption of microbial cells onto its surface, where it can penetrate the cell membrane and disrupt its integrity. The antimicrobial potential of GO is significantly enhanced by the presence of oxygen-containing functional groups on its surface. These groups can form strong electrostatic interactions with bacterial cell walls, altering the permeability of the cell membrane and allowing for the leakage of intracellular contents. Furthermore, GO's large surface area allows it to carry other antimicrobial agents, including antibiotics, peptides,

or metal nanoparticles, improving their delivery and efficacy [81]. This combination of mechanical damage and drug delivery capabilities makes GO a powerful tool for combating bacterial infections, particularly those involving multidrug-resistant strains. In addition to its antimicrobial properties, graphene oxide has shown promise as a carrier for gene delivery systems and as a platform for various biomedical applications. GO's biocompatibility and the ability to functionalize its surface with specific targeting ligands allow for the development of highly efficient drug and gene delivery systems that can target specific tissues or pathogens, reducing off-target effects and increasing therapeutic outcomes. Beyond graphene oxide, other carbon-based nanoparticles like CNTs and graphene QDs also display significant antimicrobial properties. CNTs can interact with bacterial cell membranes by physically inserting themselves into the membrane, causing mechanical damage. Similarly, graphene quantum dots, due to their unique fluorescence properties and small size, have been explored for applications in imaging, drug delivery, and antimicrobial therapy. Despite their promising antimicrobial potential, carbon-based nanoparticles, particularly graphene oxide, also pose some challenges. Concerns about their toxicity and biodegradability in the human body and environment must be addressed for their safe application. As a result, ongoing research is focused on developing safer and more biocompatible derivatives, functionalizing GO with additional materials, and evaluating their long-term effects in medical and environmental settings [82,83].

2.5. Composite Nanoparticles

Composite nanoparticles are nanoscale structures made by combining two or more different materials or components. This integration at the nanoscale allows the resulting nanoparticles to exhibit unique properties or functionalities that are unattainable with the individual materials alone. The synergy between the combined materials enhances their performance and broadens their potential applications across various fields, including medicine, biotechnology, and materials science [70].

Metal–polymer composite nanomaterials combine enhanced antimicrobial efficacy with improved biocompatibility. These composites are designed for controlled release of metal ions, which are toxic to microorganisms, disrupting their cellular processes and leading to cell death. Additionally, the metal nanoparticles on the composite's surface can directly interact with microbes, damaging cell membranes and interfering with microbial functions. Some metal–polymer composites exhibit broad-spectrum antimicrobial activity, making them effective against various bacteria, fungi, and other microorganisms. Their unique combination of properties makes them highly suitable for applications in medical devices, antimicrobial coatings, and other technologies requiring both biocompatibility and potent antimicrobial performance [84].

Metal–metal oxide composites combine different metals or metal oxides to achieve synergistic effects that enhance antimicrobial activity. This combination often results in improved efficacy, as the metal nanoparticles provide rapid antimicrobial action while the metal oxide nanoparticles sustain and extend this activity over time. The metal component releases ions, such as Ag^+ or Cu^{2+} , which are toxic to microorganisms and can disrupt their cell membranes, proteins, and DNA, ultimately causing cell death. Metal oxide NPs, such as zinc oxide (ZnO) and titanium dioxide (TiO_2), further enhance antimicrobial performance through their photocatalytic properties. When exposed to UV or visible light, these nanoparticles generate ROS that damage microbial cells by disrupting cellular components. The combined actions of metal ions and photocatalytic ROS production make metal–metal oxide composites highly effective in applications requiring broad-spectrum antimicrobial activity and long-lasting performance [17,35].

Hybrid lipid–polymer nanoparticles are engineered to combine the advantages of both lipid- and polymer-based nanoparticles, offering improved stability, enhanced cellular uptake, and controlled drug release. The integration of lipids and polymers creates a synergistic effect, where the lipid component facilitates efficient cellular uptake, while the polymer component ensures controlled release kinetics and structural stability. These nanoparticles are ideal carriers for antimicrobial agents, including antibiotics, antimicrobial peptides, and other bioactive compounds. The lipid core protects the encapsulated agents from degradation, allowing for gradual and sustained release, which optimizes therapeutic efficacy. This controlled delivery system ensures prolonged antimicrobial activity, making hybrid lipid–polymer nanoparticles highly effective for applications in targeted drug delivery, infection control, and enhanced treatment outcomes [85,86].

3. Mechanisms of Antibiotic Resistance

3.1. Enzyme Production (e.g., Beta-Lactamases)

The enzymatic degradation of antibiotics, particularly through the production of beta-lactamases, remains one of the most pervasive mechanisms of resistance. Beta-lactamases hydrolyze the beta-lactam ring, rendering antibiotics such as penicillin, cephalosporins, and carbapenems ineffective [87]. The rise of extended-spectrum beta-lactamases (ESBLs) and metallo-beta-lactamases (MBLs) in Gram-negative pathogens, including *Escherichia coli* and *Klebsiella pneumoniae*, poses a significant challenge [88,89].

Nanotechnology offers promising solutions to counteract this resistance mechanism. Silver nanoparticles (AgNPs), particularly those capped with specific inhibitors, have been shown to neutralize beta-lactamase activity [90]. This is achieved through the disruption of bacterial membranes and enhanced delivery of antibiotics that would otherwise be degraded by these enzymes [91,92]. Additionally, encapsulating beta-lactam antibiotics within nanoparticles protects them from enzymatic degradation, ensuring higher therapeutic efficacy. Recent studies demonstrate that nanoparticles functionalized with beta-lactamase inhibitors provide synergistic effects, further combating resistant strains [15,93,94].

3.2. Efflux Pumps and Reduced Permeability

Efflux pumps, which actively expel antibiotics from bacterial cells, are another major resistance mechanism. Systems like AcrAB-TolC in *Escherichia coli* and MexAB-OprM in *Pseudomonas aeruginosa* contribute to multidrug resistance (MDR), significantly reducing the intracellular concentration of antibiotics and rendering treatments ineffective. Reduced permeability, often caused by modifications in bacterial outer membrane proteins or porins, further compounds the problem by limiting drug entry into the bacterial cell.

Nanoparticles offer an innovative approach to overcoming these barriers. Mesoporous silica nanoparticles, co-loaded with antibiotics and efflux pump inhibitors, have been shown to bypass these mechanisms, delivering drugs directly to bacterial cells and restoring antibiotic efficacy [95]. Similarly, polymeric nanoparticles encapsulating efflux pump inhibitors such as phenylalanine-arginine β -naphthylamide (PA β N) can effectively target resistant bacteria. By increasing the retention of antibiotics within bacterial cells, these nanoparticle systems overcome the challenges posed by efflux pumps and reduced permeability [13,96–98].

3.3. Alterations in Target Sites

Bacterial mutations that alter the binding sites of antibiotics represent a critical challenge in antimicrobial therapy. For example, mutations in penicillin-binding proteins (PBPs) in methicillin-resistant *Staphylococcus aureus* (MRSA) reduce the binding affinity of beta-lactam antibiotics, while mutations in DNA gyrase and topoisomerase IV confer

resistance to fluoroquinolones. These alterations diminish the effectiveness of antibiotics, even at high doses.

Functionalized nanoparticles, such as gold nanoparticles (AuNPs) conjugated with antibiotics, offer a promising solution to this issue. AuNPs enhance the binding efficiency of antibiotics to their targets, even in strains with altered PBPs or gyrase enzymes [93]. Additionally, rationally designed nanoparticles that specifically target mutant proteins have been developed to circumvent resistance. For instance, selenium nanoparticles (SeNPs) disrupt oxidative stress responses in resistant strains of *E. coli* and *Pseudomonas aeruginosa*, enhancing the overall efficacy of antibiotics [95,99].

3.4. Biofilm Formation and Resistance

Biofilm formation represents a significant obstacle in the treatment of bacterial infections. These complex communities of bacteria are embedded within an extracellular polymeric substance (EPS), which acts as a protective barrier against antibiotics and the host immune response. Biofilms are notoriously difficult to eradicate, as the dense matrix reduces the penetration of antibiotics and alters local microenvironments, such as pH and oxygen availability, creating a heterogeneous population of bacteria with varying levels of resistance. Within biofilms, bacterial cells exhibit heightened tolerance to antibiotics, often requiring doses that exceed the toxicity threshold for the host. Furthermore, the biofilm lifestyle promotes the horizontal transfer of resistance genes, accelerating the spread of antimicrobial resistance.

Nanotechnology offers a promising avenue for combating biofilm-associated resistance. Functionalized nanoparticles have demonstrated the ability to disrupt biofilm formation and eradicate established biofilms. For instance, nanoparticles incorporating bioactive compounds, such as essential oils or antibiotics, can penetrate biofilms more effectively than traditional antibiotics alone. Metallic nanoparticles, including those based on silver or zinc oxide, exhibit inherent antibiofilm properties due to their ability to disrupt bacterial cell membranes and generate ROS [100,101].

Hybrid nanosystems that combine antibiotics with metal nanoparticles or polymeric carriers have shown synergistic effects, increasing the efficacy of treatments against biofilm-forming bacteria while minimizing adverse effects on mammalian cells. For example, graphene oxide and silver nanoparticle composites enhance biofilm eradication by disrupting both bacterial cells and the EPS matrix. These approaches hold potential not only for treating biofilm-related infections but also for preventing their formation on medical devices, such as catheters and implants, where biofilms commonly develop [102,103].

3.5. Quorum Sensing and Antibiotic Resistance

Quorum sensing (QS) is a bacterial communication system that relies on the production, release, and detection of signaling molecules called autoinducers. QS regulates critical behaviors such as virulence factor production, biofilm formation, and resistance to antibiotics. By coordinating these activities at the population level, bacteria can mount more effective defenses against treatments. Interrupting QS pathways is an innovative strategy to combat bacterial resistance, as it disarms the pathogens rather than killing them, reducing the selective pressure for resistance development [104]. Nanoparticles functionalized with quorum sensing inhibitors (QSIs) offer a targeted approach to disrupt these pathways. For example, polymeric nanoparticles encapsulating QSIs can deliver these compounds directly to bacterial cells, enhancing their effectiveness while minimizing off-target effects [105–107].

Metallic nanoparticles, such as those based on silver or gold, have also been shown to interfere with QS by binding to signaling molecules or receptors, preventing the co-

ordination of bacterial behavior [108,109]. Additionally, biofunctionalized nanoparticles incorporating natural QSIs, such as plant-derived phenolic compounds, provide an eco-friendly and sustainable approach to mitigating QS-mediated resistance [110,111]. Beyond bacterial infections, QS inhibition using nanotechnology has potential applications in preventing biofilm formation on industrial and medical surfaces. Moreover, combining QS inhibition with conventional antibiotics can synergistically enhance treatment efficacy, particularly in multidrug-resistant bacterial populations [109]. The mechanisms of antibiotic resistance can be categorized into intrinsic, adaptive, and acquired resistance. Intrinsic resistance includes natural bacterial defenses such as efflux pumps and reduced membrane permeability. Adaptive resistance arises from environmental stressors, leading to biofilm formation or temporary genetic modifications. Acquired resistance occurs through horizontal gene transfer or spontaneous mutations, allowing bacteria to develop resistance against multiple antibiotics, (Figure 1).

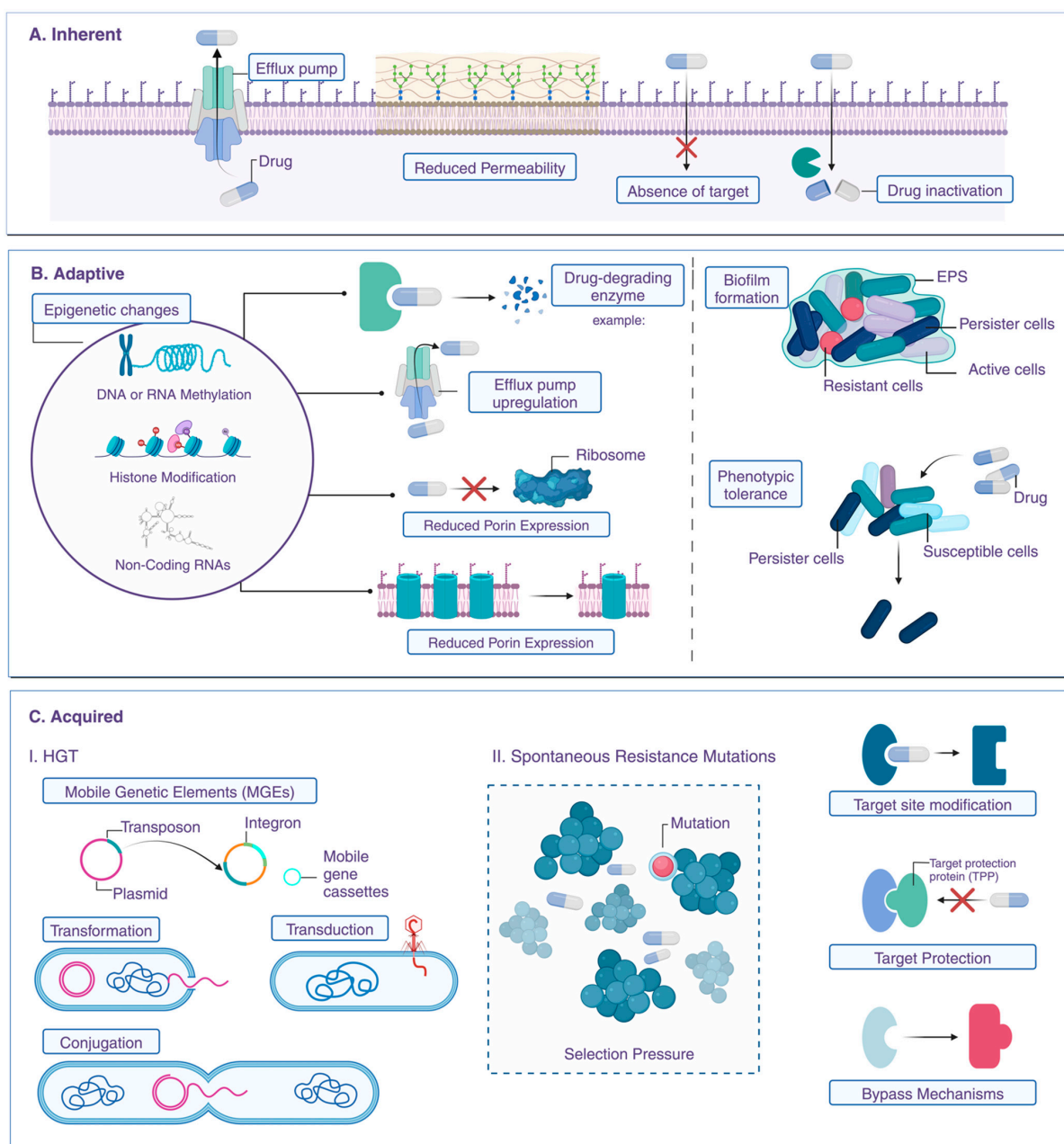


Figure 1. Mechanisms of antimicrobial resistance: inherent, adaptive, and acquired. This figure categorizes antimicrobial resistance into intrinsic, adaptive, and acquired mechanisms. (A) Intrinsic

resistance: Innate features, such as efflux pump activity, reduced membrane permeability, drug inactivation, and the absence of specific targets, provide baseline resistance, exemplified by reduced porin expression in Gram-negative bacteria. **(B) Adaptive resistance:** These transient mechanisms, reversible after the removal of selective pressure, include biofilm formation, persister cell generation, phenotypic tolerance, and epigenetic changes like DNA methylation and histone-like protein modifications that regulate gene expression. Enhanced efflux pump activity and reduced porin expression further aid bacterial survival under stress. **(C) Acquired resistance:** **(I) Horizontal gene transfer (HGT)** involves mobile genetic elements such as plasmids, transposons, and integrons, facilitating the spread of resistance genes via transformation, conjugation, or transduction. **(II) Spontaneous resistance mutations** result from random genetic changes under antibiotic pressure, modifying target sites, protecting targets, or creating bypass pathways, as seen in mutations like *gyrA* (fluoroquinolone resistance) and *rpoB* (rifampin resistance). These mechanisms demonstrate the diverse strategies bacteria use to evade antimicrobial therapies.

4. Challenges in Developing New Antibiotics

4.1. Rapid Resistance Development

The rapid emergence of resistance to newly developed antibiotics highlights the urgent need for innovative therapeutic strategies. Resistance mechanisms such as porin mutations, hyperactive efflux pumps, and enzymatic degradation can render even advanced antibiotics ineffective within a short time frame. For example, ceftazidime-avibactam, a combination antibiotic targeting ESBL-producing pathogens, has encountered resistance due to mutations in porins and beta-lactamases [96].

Nanoparticles address this challenge by providing a versatile platform for co-delivery of antibiotics and adjuvants. For instance, lipid nanoparticles (LNPs) encapsulating rifampin and vancomycin improve drug solubility, stability, and bioavailability, enhancing their ability to target biofilm-associated pathogens such as *Staphylococcus epidermidis* [93,112]. Biofilm penetration is particularly significant, as biofilms are known to provide a protective environment that enables bacteria to withstand high concentrations of antibiotics. Nanoparticles have shown the ability to disrupt biofilms and deliver drugs directly to bacterial cells within these structures, addressing one of the most challenging aspects of resistance. Furthermore, studies on composite nanoparticles, such as those combining nano zinc oxide and nano propolis, have demonstrated the potential to mitigate the development of resistance by targeting multiple bacterial pathways simultaneously [113]. This multifaceted approach reduces the likelihood of bacteria developing resistance to nanoparticle-based therapies, offering a sustainable solution to the rapid emergence of resistance [114].

4.2. Limited Pharmaceutical Innovation and Drug Pipelines

The economic and regulatory challenges associated with antibiotic development have contributed to a decline in pharmaceutical innovation. High costs of research and development, coupled with low financial returns due to restricted use of antibiotics to prevent resistance, discourage investment in this critical area. As a result, the antibiotic pipeline remains insufficient to meet the growing threat of resistance.

Nanotechnology provides a cost-effective alternative by enhancing the activity of existing antibiotics and reducing the need for entirely new drug classes. Rationally designed nanoparticles functionalized with antibiotics have been shown to maintain antimicrobial efficacy while minimizing toxicity to mammalian cells, making them a viable option for therapeutic development [115,116]. Additionally, public-private partnerships and funding initiatives are increasingly focusing on nanoparticle-based solutions to revitalize the antibiotic pipeline [96]. Moreover, nanoparticle-based therapies have demonstrated the ability to overcome barriers associated with traditional drug development. For example,

graphene oxide composites doped with silver nanoparticles have been utilized in medical devices to prevent bacterial adhesion and biofilm formation, reducing the need for systemic antibiotic use [117]. These innovations not only address the problem of resistance but also minimize the economic and regulatory hurdles associated with conventional antibiotics.

5. Mechanisms of Action of Nanoparticles Against Bacteria

One primary mechanism is the disruption of bacterial membranes, a process where nanoparticles directly interact with the bacterial cell wall, which is typically negatively charged. Nanoparticles, especially those with cationic properties, bind to these surfaces and cause physical damage. This can lead to increased membrane permeability or complete structural rupture, resulting in cell lysis. Nanoparticles with sharp edges, such as graphene oxide, can physically slice through bacterial membranes, while others, such as silver nanoparticles, chemically alter membrane integrity. This approach is particularly effective against a wide range of bacteria, including Gram-positive and Gram-negative strains, as it relies on physical interactions rather than specific biochemical pathways that bacteria often develop resistance against [26,118]. Another significant antimicrobial mechanism is the generation of ROS, which is particularly prominent in metal and metal oxide nanoparticles such as silver, zinc oxide, and titanium dioxide. These nanoparticles catalyze the formation of ROS, including hydroxyl radicals, superoxide ions, and hydrogen peroxide. ROS exerts antimicrobial effects by inducing oxidative stress, which damages bacterial membranes, proteins, and genetic material. The oxidative damage caused by ROS is often irreversible, leading to bacterial death. For photocatalytic nanoparticles like titanium dioxide, ROS production is enhanced under ultraviolet or visible light, making them highly effective in sterilization and disinfection applications [51,118]. Nanoparticles also serve as advanced drug carriers, enabling targeted delivery and controlled release of antibiotics. By encapsulating antibiotics within their structures, nanoparticles protect the drugs from enzymatic degradation and enhance their stability. Functionalized nanoparticles can be directed to specific infection sites, such as biofilms, which are often resistant to conventional antibiotics. Once at the site of infection, nanoparticles enable a sustained and controlled release of antibiotics, maintaining therapeutic concentrations over extended periods [119]. This targeted delivery reduces systemic toxicity, minimizes side effects, and allows for lower antibiotic dosages, thereby decreasing selective pressure for resistance development. In addition to their intrinsic antimicrobial properties, nanoparticles can enhance the efficacy of existing antibiotics through synergistic effects. By disrupting bacterial membranes, nanoparticles facilitate the entry of antibiotics into bacterial cells, where they can exert their effects more efficiently. Some nanoparticles also inhibit bacterial efflux pumps, preventing the bacteria from expelling antibiotics and rendering them more effective. Furthermore, nanoparticles can penetrate and disrupt biofilms, which are a major barrier to antibiotic treatment in chronic infections. Combining nanoparticles with antibiotics, such as silver nanoparticles with vancomycin or ampicillin, has shown significantly improved antibacterial activity, even against resistant strains. Overall, the multifaceted mechanisms employed by nanoparticles make them powerful tools in combating bacterial infections. Their ability to bypass traditional resistance mechanisms, enhance the activity of antibiotics, and target infection sites with precision highlights their potential in modern medicine. As research progresses, further optimization and clinical application of these mechanisms will pave the way for more effective treatments against antibiotic-resistant bacteria [26,120,121].

6. Recent Advances and Case Studies

6.1. Case Studies of Successful Nanoparticle Applications

Nanoparticles have demonstrated significant potential in overcoming antibiotic resistance through their multifaceted mechanisms of action. Among the most extensively studied are silver nanoparticles (AgNPs), which exhibit broad-spectrum antimicrobial activity [122]. AgNPs effectively combat (MRSA), carbapenem-resistant *Klebsiella pneumoniae*, and vancomycin-resistant *Enterococcus faecium*. These particles function by disrupting bacterial membranes, inducing reactive oxygen species (ROS) production, and interfering with bacterial metabolic processes [88]. Furthermore, their ability to inhibit biofilm formation makes them invaluable for managing chronic and device-associated infections [91,123].

Gold nanoparticles (AuNPs) also hold promise, particularly in combination with antibiotics. Ciprofloxacin-conjugated AuNPs, for example, have shown enhanced efficacy against multidrug-resistant Gram-negative bacteria by bypassing resistance mechanisms like efflux pumps and reduced permeability [93]. Similarly, selenium nanoparticles (SeNPs) have been employed to enhance antibiotic activity against resistant strains of *Escherichia coli* and *Pseudomonas aeruginosa*. These particles disrupt oxidative stress responses and bacterial bioenergetics, leading to synergistic antimicrobial effects [95]. Another innovative approach involves the use of nanoemulsions that combine essential oils with conventional antibiotics. These formulations leverage the natural antimicrobial properties of essential oils while improving the solubility and stability of antibiotics. Preclinical studies have demonstrated their effectiveness in treating respiratory and systemic infections caused by resistant pathogens, underscoring their potential for clinical application [96,124].

6.2. Notable Advances in Clinical Trials and Preclinical Studies

Significant progress has been made in the clinical and preclinical evaluation of nanoparticle-based therapies. Lipid nanoparticles (LNPs) encapsulating antibiotics such as vancomycin and rifampin have shown remarkable efficacy in treating biofilm-associated infections, including prosthetic joint infections and endocarditis [125,126]. These systems enhance drug solubility, protect the active agents from degradation, and improve penetration into biofilms, thereby overcoming a major barrier in antimicrobial therapy [113].

Mesoporous silica nanoparticles (MSNs) represent another promising development. These particles can be co-loaded with antibiotics and adjuvants such as lysozyme to achieve a dual-mode action: direct bacterial killing and disruption of biofilm structures. Preclinical studies have demonstrated their effectiveness against biofilm-forming pathogens like *Pseudomonas aeruginosa* and *Staphylococcus aureus* [95,126].

Polymeric nanoparticles, particularly those derived from biocompatible materials like chitosan, have gained attention for their intrinsic antimicrobial properties. These nanoparticles not only deliver antibiotics more effectively but also reduce systemic toxicity and side effects. Early-stage clinical trials suggest that polymeric nanoparticles could lower the required doses of antibiotics while maintaining therapeutic efficacy [93]. Additionally, graphene oxide composites doped with silver nanoparticles have been applied to medical devices such as catheters and orthopedic implants [127]. These coatings prevent bacterial adhesion and biofilm formation, significantly reducing infection rates in pilot studies. This approach has the potential to transform infection control strategies in clinical settings [117].

6.3. Nanoparticles as Antibacterial Agents in Medical Devices

The integration of nanoparticles into medical devices represents a groundbreaking advancement in preventing healthcare-associated infections. Titanium dioxide (TiO₂) nanoparticles, for instance, have been embedded into catheter surfaces to inhibit bacterial adhesion and biofilm formation [128–131]. These nanoparticles generate ROS under specific

conditions, leading to the destruction of bacterial cells without affecting human tissues. Their efficacy against multidrug-resistant strains like *Klebsiella pneumoniae* and *Acinetobacter baumannii* has been well-documented [117,132].

Silver nanoparticle-based coatings have shown promise in orthopedic implants and cardiovascular devices. These coatings exhibit dual functionality: they prevent bacterial colonization and actively disrupt biofilms. Studies on prosthetic joints and heart valves have demonstrated significant reductions in infection rates, suggesting that such nanoparticle applications could drastically improve patient outcomes [91,133].

Graphene oxide composites, doped with AgNPs, further enhance the antibacterial properties of medical devices. These composites combine the physical barrier properties of graphene oxide with the antimicrobial activity of silver nanoparticles, resulting in robust resistance to bacterial colonization. Clinical studies indicate that these materials are particularly effective in preventing device-related infections, including those caused by antibiotic-resistant bacteria [117].

Lastly, nano-functionalized materials such as zinc oxide nanoparticles (ZnO NPs) and nano-propolis composites have demonstrated antimicrobial properties when incorporated into wound dressings and surgical sutures [134]. These materials promote wound healing while simultaneously reducing the risk of infection from resistant pathogens, providing a dual benefit in post-surgical care [113,135].

7. Challenges and Limitations of Using Nanoparticles in Treating Resistant Bacteria

While nanoparticles have shown significant potential as antimicrobial agents, their use also presents several challenges and limitations that must be addressed to ensure their safe and effective application.

7.1. Potential Toxicity to Human Cells and Environmental Impact

One of the primary challenges in utilizing NPs as antimicrobial agents is their potential toxicity, which poses significant threats to human health and limits their clinical applications.

This toxicity is significantly affected by various factors such as their size, composition, surface characteristics, and aggregation behavior, making the prediction of their precise biological impact difficult [55]. The small size of NPs allows them to penetrate physiological barriers, potentially resulting in harmful biological reactions, such as organ injury and oxidative stress, ultimately inducing long-term cellular damage. For instance, a study demonstrated that the cytotoxic effect of carbon-based NPs on lung cancer cells is size-dependent cytotoxicity, emphasizing that smaller particles exhibit greater toxicity due to their enhanced cellular penetration [8,56].

NPs can enter the human body through various routes, including the skin, lungs, and intestines, causing potentially adverse effects such as cardiovascular issues, and lung inflammation. These entry pathways, in addition to their unique physical properties of the NPs, emphasize the need for a comprehensive understanding of their toxicological profiles to ensure safe and effective applications [8,55,56]. Furthermore, NPs have been demonstrated to elicit immune responses, causing inflammatory reactions or other adverse effects, which can manifest as tissue damage or chronic inflammation [57,58]. Additionally, genetic factors could play a key role in defining the body's overall response to the NP's exposure, influencing the severity and toxicity of the reaction [56].

Although biocompatibility of NPs is often estimated through in vitro assays using cell cultures, considering the various entry pathways, it is crucial to apply in vivo models for a

complete understanding of the metabolism, clearance, and toxicity in the body. This will help ensure that NPs are both effective against resistant bacteria and for human use [59,60].

Optimizing NP use is an additional significant challenge. Although the sustained release systems and targeted delivery are advantages of the NPs, it is necessary to balance these benefits carefully with the potential risks, including the emergence of antimicrobial resistance. For example, reducing the side effects of NPs while confirming effective antibacterial action, requires dose recalibration and the identification of appropriate routes of administration. This optimization depends on factors such as particle size, surface characteristics, and delivery mechanisms, and can be further complicated by genetic variability in individuals [61]. In addition to concerns regarding human health, the NP's environmental impact is also a growing issue. Because of their small size and distinctive properties, NPs can act upon diverse components of natural ecosystem, possibly disrupting ecological balance, accumulating in the food chain, and impacting species, leading to wildlife exposures and humans alike. For instance, studies on materials such as silver NPs (Ag NPs) and [62] titanium dioxide NPs (TiO₂ NPs) have shown their toxicity to aquatic and terrestrial organisms, disrupting ecosystems and biodiversity [55]. Extended exposure by the NPs sub-lethal doses has also been found to promote genetic mutations in bacteria, speeding the emergence of antibiotic resistance. Consequently, there is a demand for a strict regulation on NPs waste disposal in the environment to mitigate these risks [8].

7.2. Regulatory and Manufacturing Challenges

7.2.1. Ensuring Consistent Quality and Safety in Production

A significant challenge in advancing nanomedicines and nanomedical devices (NMDs) is the need to comply with strict regulatory standards, which are essential for ensuring their safety, efficacy, and quality. These standards mandate comprehensive preclinical and clinical evaluations, including detailed toxicity and safety assessments. Due to the unique size, structure, and surface characteristics of nanomaterials, their toxicity profiles can vary substantially from those of conventional materials. As a result, specialized testing methods are required to evaluate acute, subacute, chronic, genotoxic, immunotoxic, and environmental toxicity. Such tests are essential for understanding the potential biological and environmental impacts of nanomedicines and NMDs [20]. To meet these regulatory standards, safety evaluations typically involve both *in vitro* and *in vivo* studies to assess biocompatibility, as well as pharmacokinetic properties, such as absorption, distribution, metabolism, and excretion. These evaluations must adhere to Good Laboratory Practices (GLPs) and Good Manufacturing Practices (GMPs) to ensure consistency and reliability throughout testing and production. While these rigorous measures reduce uncertainties in the regulatory process, they also increase the time and cost associated with research and development, presenting a significant barrier to market entry. However, meeting these regulatory requirements is essential to ensure the safe and effective delivery of nanomedicines and NMDs. Moreover, variability in batch-to-batch synthesis can complicate reproducibility and scalability, further complicating production processes [55].

7.2.2. Factors Affecting the Efficient Production of Nanoparticles

Several factors, including salt concentration, pH levels, contact duration, and temperature, can significantly impact the efficient production of high-yielding NPs. It is crucial to optimize the physicochemical properties, such as size and shape, especially when NPs are intended for biological applications. Additionally, environmentally friendly green synthesis methods for nanoparticle production pose further challenges for the commercial scale-up of these technologies [8,55].

7.2.3. Regulatory Approval Challenges

While the FDA has evaluated and approved several nanoparticle-based products, the regulatory process for nanomedicine remains complex. The FDA anticipates significant growth in the use of NPs in therapeutic applications. However, effective regulatory standards and testing protocols must be developed to address the unique challenges posed by NPs. The FDA's National Center for Toxicological Research (NCTR) focuses on assessing the biological effects and toxicity of NPs to ensure their safety and efficacy before approval. This includes conducting in vitro and in vivo studies, immunotoxicity assessments, and establishing global standards [63]. Furthermore, compared to conventional antibiotics, the approval process for nanomaterial-based treatments may delay their clinical availability. The widespread use of nanoparticle microbial compounds remains limited until these regulatory challenges are resolved and standardized guidelines are established [8,55,64].

7.3. Cost and Accessibility of Nanotechnology-Based Treatments

Balancing Advanced Technology with Affordability and Scalability

The production of nanomedicines requires advanced analytical techniques, such as dynamic light scattering and electron microscopy, to accurately characterize nanomaterials. These methods ensure consistency in particle size, shape, and surface characteristics, which are crucial for maintaining the quality and safety of the final product. However, the complexity of these requirements increases both the cost and time needed for production [55]. The introduction of nanotechnology-based treatments into the market faces significant challenges, particularly concerning cost and accessibility. The development process is often slower and more expensive than conventional antibiotics, delaying their availability for clinical use [65]. Additionally, costs associated with NPs, particularly when using environmentally friendly methods, can make large-scale manufacturing more difficult and expensive. Scaling up production while maintaining strict quality and safety standards remains an ongoing challenge [8].

8. Future Directions in Nanotechnology for Combating Antibiotic Resistance

8.1. Emerging Nanoparticle Designs New Materials and Hybrid Nanoparticles for More Effective Antibacterial Action

Hybrid nanomaterials, or composite-based nanomaterials, are a breakthrough in nanotechnology. These materials combine metal-based, carbon-based, and organic components to enhance antibacterial properties. By exploiting the synergistic effects between different materials, hybrid nanomaterials overcome key limitations of single-component NPs, such as instability and poor biocompatibility. This makes them particularly promising for improving the effectiveness of antibacterial treatments. Surface modification of inorganic NPs, such as gold, titanium dioxide, and silver, using organic polymers like polyethylene glycol or polydopamine, represents a significant advancement in nanotechnology. These modifications enhance the NP dispersibility in aqueous solutions, improve their physicochemical properties (such as size and charge), and enable targeted functionalization for antibacterial applications [136,137]. As a result, these surface modifications not only increase antimicrobial effectiveness but also reduce cytotoxicity, which is crucial for their safe use in clinical settings. Another promising avenue is the use of metal–organic frameworks (MOFs), which offer unique characteristics such as tunable structures, high porosity, and large surface areas. MOFs serve as versatile platforms for drug delivery and antimicrobial applications. For example, MOF-based nanovehicles facilitate nucleus-targeted drug delivery, while composite coatings on medical implants, incorporating MOFs and sulfonated hyaluronic acid, improve biocompatibility and inhibit bacterial colonization [138]. In parallel, metal

and metal oxide NPs exhibit a complex mechanism of action against bacterial cells, which helps reduce the likelihood of resistance development. When these NPs are combined with antibacterial drugs, they form hybrid systems that not only enhance bactericidal activity but also restore the efficacy of antibiotics. This approach has several advantages, including reducing the necessary therapeutic doses, minimizing dose-dependent toxicity, delaying the emergence of resistance, and shortening treatment durations [139]. Collectively, these advancements underscore the potential of hybrid nanomaterials to address critical challenges in antibiotic resistance. By optimizing material composition and functionalization, these next-generation NPs represent a paradigm shift in antibacterial therapy, paving the way for more effective and sustainable solutions [138,139].

8.2. Personalized Nanomedicine Tailoring Nanoparticle Treatment to Individual Bacterial Infections and Patient Needs

Personalized nanomedicine is emerging as a critical strategy in the battle against antibiotic resistance. By utilizing nanotechnology, healthcare providers can develop treatments that are specifically tailored to the genetic and immune profiles of individual patients. This customization enhances therapeutic effectiveness and reduces the risk of developing resistance. NPs can be engineered to selectively target specific bacterial strains while also interacting with the patient's immune system, providing a precise, targeted therapeutic approach. This level of personalization overcomes many limitations of conventional antibiotics, ensuring more effective infection control and improved patient outcomes [15]. The integration of nanotechnology with personalized medicine has led to significant advancements, particularly in the development of tailored drug delivery systems. These systems employ NPs that can target bacterial infections with precision, adjusting their release mechanisms based on the patient's specific needs. By enabling targeted delivery, these systems minimize the side effects typically associated with broad-spectrum antibiotics. Recent studies have demonstrated the ability of nanoformulations to optimize drug delivery by considering factors such as the patient's genetic profile, immune responses, and the specific bacterial strain involved. This approach not only enhances treatment efficacy but also reduces the risk of antibiotic resistance by ensuring that the right drug is delivered to the right site at the optimal time [15,140].

One of the key innovations in personalized nanomedicine is the use of nano-sensors and nanodevices to detect bacterial biomarkers. These devices can quickly identify the type of pathogen and its resistance profile, allowing for faster and more accurate diagnosis. By employing nanotechnology-based genomic sequencing methods, clinicians can obtain detailed genetic information about the bacterial strain, enabling them to tailor antibiotic treatments more effectively. These techniques provide a rapid and cost-effective alternative to traditional diagnostic methods, improving the precision of antibiotic selection and reducing the risk of resistance development [138].

Furthermore, the integration of pharmacogenomics with nanotechnology plays a vital role in personalizing treatment. By analyzing the genetic profiles of both the patient and the bacterial pathogen, nanoformulations can be designed to deliver drugs that are best suited to the patient's biological characteristics. This fusion of genomics and nanotechnology aims to create error-free and highly targeted therapeutic systems that address the specific resistance mechanisms of pathogens, providing a more effective means of combating antibiotic-resistant infections [138].

Despite the promising advancements in personalized nanomedicine, several challenges remain in translating these technologies into clinical practice. One major hurdle is the scalability of nanomedicine, particularly the production of high-quality nanoparticle-based therapies in large quantities. Additionally, the high cost of development and manufacturing, combined with regulatory obstacles, poses significant barriers to the widespread

use of these treatments in combating antibiotic-resistant infections. Ethical concerns, such as patient participation in clinical trials for personalized treatments, also need to be addressed. These challenges highlight the necessity for ongoing research, collaboration, and innovation to ensure that personalized nanomedicine can be fully realized and applied globally [15,138].

As personalized nanomedicine advances, theranostics—an integrated approach combining both diagnostic and therapeutic functions—emerges as a promising direction. Theranostic systems enable real-time monitoring of treatment efficacy while delivering therapeutics directly to infection sites. In bacterial infections, these systems ensure that antibiotics are delivered precisely, reducing unnecessary exposure to the drug and minimizing the risk of resistance development. Furthermore, recent developments in optical imaging-guided nanotheranostics allow clinicians to track treatment progress and adjust therapies based on real-time feedback from the patient's response, offering a dynamic and highly targeted treatment strategy [138].

In summary, personalized nanomedicine offers a transformative approach to treating antibiotic-resistant infections by providing tailored, precise, and effective treatments. Through the integration of smart drug delivery systems, nanosensors, genetic profiling, and theranostic, nanotechnology is paving the way for more individualized, efficient, and sustainable solutions to combat the growing challenge of antibiotic resistance. Moving forward, addressing the challenges related to production scalability, cost, and ethical considerations will be essential to fully realizing the potential of personalized nanomedicine in clinical settings [138,140].

8.3. Integration with Other Therapeutic Modalities Combining Nanoparticles with Phage Therapy, CRISPR, and Immunotherapy

The integration of NPs with phage therapy, CRISPR-based systems, and immunotherapy offers a promising strategy for addressing antibiotic resistance. NPs serve as a versatile platform that can enhance the efficacy, stability, and targeted delivery of these therapeutic agents. By combining these modalities, NPs can overcome significant clinical challenges, such as limited drug delivery and off-target effects, ensuring more effective treatments against resistant bacteria [141–143].

8.3.1. Combining Nanoparticles with Phage Therapy

Phage-based nanotechnology offers an innovative approach to combat MDR bacterial infections by combining bacteriophages with NPs. This combination enhances antimicrobial effectiveness by improving phage stability, detection, and targeted delivery, especially for managing infections associated with medical implants. Applications such as phage–NP-based biosensors for bacterial detection and typing, phage–NP-mediated focalized therapy, and encapsulation of phages for improved therapeutic outcomes demonstrate the versatility of this technology (Figure 2). For example, the irradiation of gold nanoparticle (AuNP)-coated M13 phages with a 532 nm laser has shown a significant reduction in *E. coli* populations in liquid cultures, ranging from 21% to 64% [141]. These findings highlight the potential of phage-based nanomaterials, such as phanorods, in treating localized infections or wounds caused by MDR bacteria. Future research should focus on advancing nanoparticle design, optimizing production processes for scalable applications, and conducting in vivo studies to fully explore the clinical potential of this promising technology. Additionally, nanoparticle-based lysin delivery systems are gaining attention as a complementary approach to phage therapy. Lysin-loaded chitosan nanoparticles offer a novel strategy for targeted antibacterial therapy. Lysins, enzymes derived from bacteriophages, are known for their ability to degrade bacterial cell walls, effectively killing bacteria without causing resistance development. When encapsulated in chitosan nanoparticles, lysins can be pro-

tected from premature degradation, allowing for more controlled and efficient delivery to the infection site. This system also provides enhanced stability and improved therapeutic outcomes, especially when applied in localized infections caused by multidrug-resistant pathogens. Research into lysin-loaded chitosan nanoparticles is still in the early stages, but the potential for this system to work synergistically with phage-based therapies could offer a promising route for combating resistant infections [144,145].

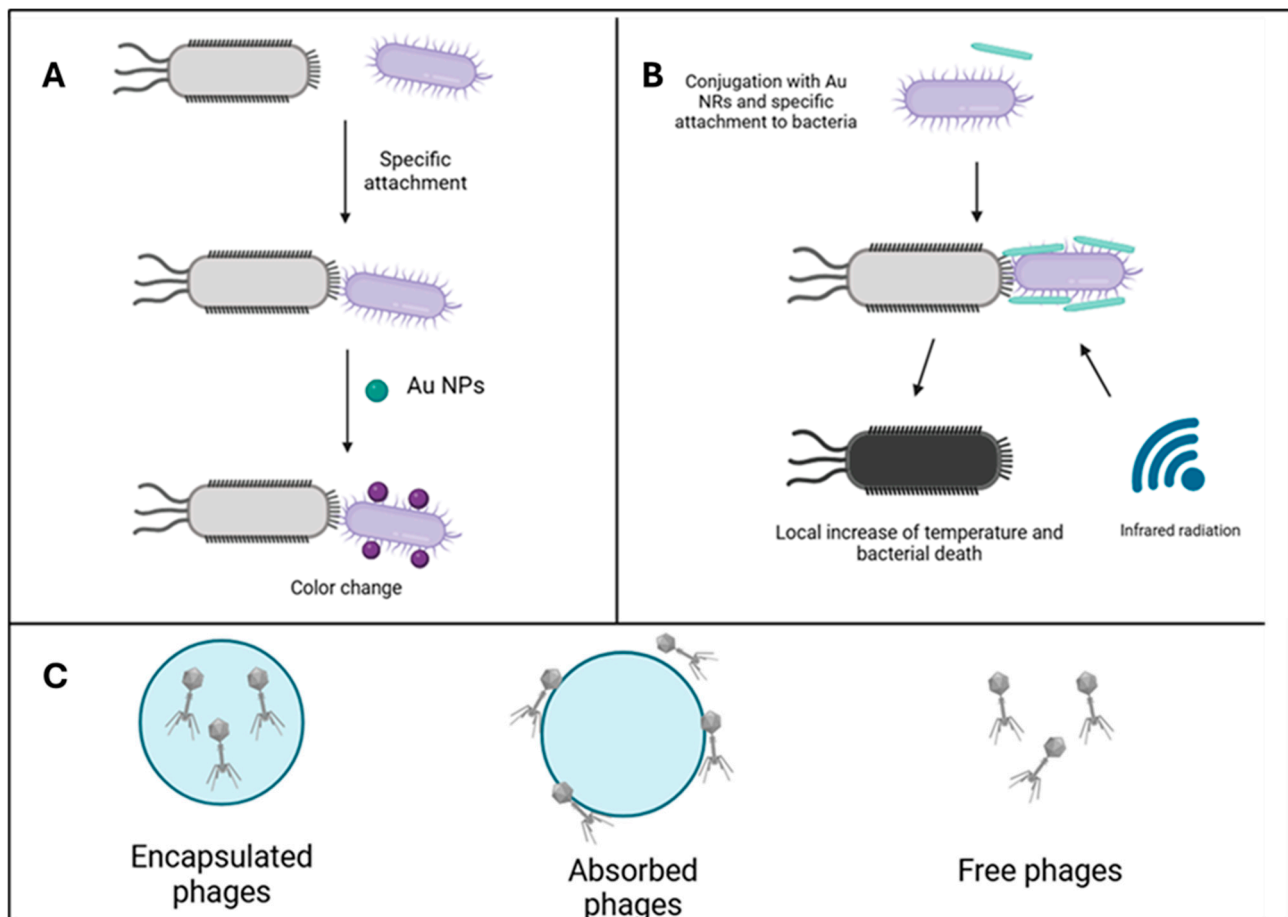


Figure 2. Examples of integrating nanotechnology with phages. (A) employing phages conjugated with gold nanoparticles (AuNPs) for bacterial detection, sensing, and typing, utilizing their surface plasmon resonance properties to induce color changes; (B) using phages combined with gold nanorods (AuNRs) for targeted photothermal therapy; and (C) encapsulating or adsorbing phages within nanoparticles (NPs) and microparticles (MPs) to enhance the clinical efficacy of phage therapy compared to free phage administration.

8.3.2. Combining Nanoparticles with CRISPR Therapy

Recent research is focusing on integrating nanotechnology with other therapeutic modalities to combat antibiotic resistance. NPs, such as lipids, polymeric, and gold NPs (Figure 3), show promising potential in enhancing the delivery of CRISPR systems, improving the stability of Cas9 mRNA, and increasing gene-editing efficiency. Strategies like Selective Organ Targeting (SORT) are used to precisely direct NPs to target tissues such as the liver, lungs, and spleen, enhancing treatment efficacy. Additionally, cationic lipid systems and liposome-templated hydrogel NPs (LHNPs) demonstrate high effectiveness in targeting cancer cells and inhibiting tumor growth in animal models, paving the way for improved gene therapies and combating antibiotic resistance [143].

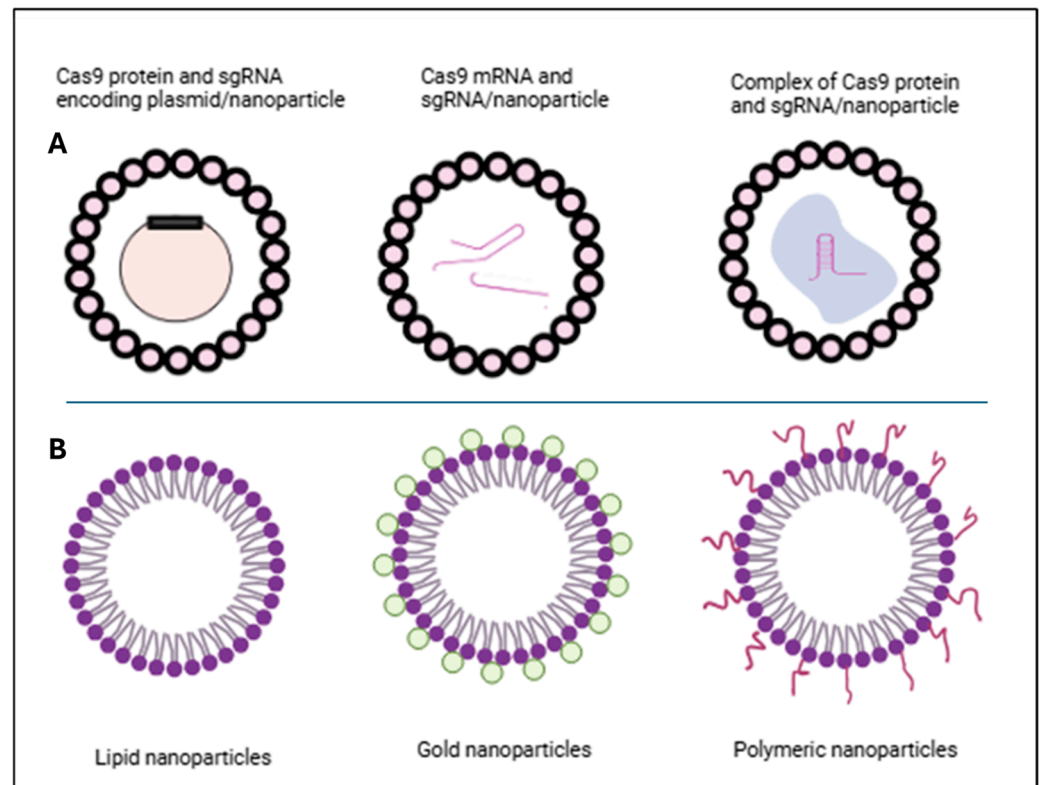


Figure 3. Nanoparticles (NPs) are used for drug and gene delivery to combat bacterial infections. (A) NPs can encapsulate different forms of CRISPR-Cas9, including Cas9 protein with sgRNA-encoding plasmids, Cas9 mRNA with sgRNA, or a complex of Cas9 protein and sgRNA. (B) Common NPs for CRISPR-Cas9 delivery include lipid NPs, polymeric NPs, and gold NPs.

Future research should focus on developing NPs with enhanced biocompatibility, precise targeting, and scalability. These advancements will be essential in translating nanoparticle-CRISPR systems into effective clinical therapies, helping to combat the global challenge of antibiotic resistance.

8.3.3. Combining Nanoparticles with Immunotherapy

To address the challenges of antibiotic-resistant bacteria, nanomaterial-based vaccines with excellent biocompatibility, extended circulation, and targeted performance offer promising solutions. These multifunctional nanoplatforms can integrate various therapeutic strategies, including immunotherapy, to enhance the body's immune response against pathogens. Recent advances in nanotechnology have led to the development of smart antibacterial platforms with immunomodulatory properties, enabling the controlled release of therapeutic agents directly at infection sites. This targeted delivery not only improves pathogen clearance but also reduces medication dosage and minimizes adverse effects on healthy tissues.

Furthermore, NPs are effective in breaking down complex biofilm structures and eradicating mature bacterial biofilms, thereby enhancing the local immune microenvironment and stimulating the immune system. These nanoplatforms can boost immune responses by promoting immunogenic cell death (ICD) in bacteria, which triggers immune activation and promotes the migration of lymphocytes into tissues. As a result, nanotherapeutic strategies can support the maturation of dendritic cells (DCs), regulate macrophage polarization, and activate T cells, all while facilitating long-term immune monitoring to prevent recurrent infections [142].

8.3.4. Combining Nanoparticles with Peptide

Peptide-functionalized nanoparticles are emerging as a promising tool in the fight against bacterial infections, offering enhanced specificity, targeting, and therapeutic efficacy. By conjugating peptides—small chains of amino acids—with nanoparticles, these multifunctional platforms can exploit the natural affinity of peptides for specific receptors on bacterial surfaces, allowing for targeted drug delivery. This targeted approach ensures that therapeutic agents are delivered directly to infection sites, reducing off-target effects and minimizing damage to healthy tissues. The use of peptides in nanoparticle functionalization not only enhances targeting but also improves the stability and biocompatibility of nanoparticles. Peptides can be designed to bind specifically to bacterial cell membranes, facilitating the precise localization of the drug-loaded nanoparticles. Additionally, peptide-functionalized nanoparticles can increase the internalization of the nanoparticles by bacteria, enhancing their antimicrobial efficacy [146,147].

Recent advances have demonstrated that peptide-functionalized nanoparticles are effective in combating antibiotic-resistant bacteria, as they can be engineered to disrupt bacterial cell membranes or inhibit critical biological pathways in pathogens. Moreover, these nanoparticles can be designed to cross biofilm barriers, making them an ideal solution for eradicating mature biofilms that are notoriously difficult to treat with conventional antibiotics. Peptide-functionalized nanoparticles also hold significant promise in combination with other therapeutic strategies, such as immunotherapy. By incorporating immunomodulatory peptides, these nanoparticles can not only target pathogens directly but also stimulate the immune response. They can enhance the activation of immune cells, such as dendritic cells and macrophages, improve antigen presentation, and promote T-cell activation, contributing to both the direct eradication of pathogens and long-term immune surveillance. These advances in peptide-functionalized nanoparticles represent a step forward in the development of personalized, targeted nanotherapeutic strategies, offering a powerful approach to combating bacterial infections and preventing recurrent infections [147,148].

8.3.5. Integration of Nanotechnology and 3D Printing in Drug Delivery and Personalized Medicine

The integration of nanotechnology and 3D printing, often referred to as “nanoprinting”, is revolutionizing drug delivery systems and personalized medicine. This approach enables the creation of multifunctional medical products that are specifically designed to meet individual patient needs, advancing fields such as tissue engineering and regenerative medicine [138]. By incorporating nanotechnology-based drugs into 3D printing, personalized nanomedicines can be efficiently produced, enhancing therapeutic outcomes. The use of microfluidic chips for continuous production further facilitates the clinical translation of these technologies. Additionally, combining 3D printing with biopharmaceuticals offers the potential to enhance existing therapies and foster the development of 3D culture systems for tissue engineering, paving the way for significant advances in regenerative medicine and novel therapeutic strategies [149].

9. Conclusions

Antibiotic resistance represents a formidable global health challenge, threatening the effectiveness of modern medicine and endangering essential medical procedures. The escalating prevalence of resistant infections underscores the urgency of developing innovative approaches to combat bacterial pathogens. While the traditional antibiotic pipeline has stagnated, the advent of nanotechnology offers a transformative solution to this crisis.

Nanoparticles, with their unique physicochemical properties and multi-mechanistic modes of action, present a promising alternative to conventional antibiotics. Their ability to disrupt bacterial membranes, generate reactive oxygen species, and serve as carriers for targeted drug delivery highlights their versatility in overcoming the limitations of traditional treatments. Additionally, their capacity to penetrate biofilms, bypass bacterial resistance mechanisms, and enhance the efficacy of existing antibiotics provides a significant advantage in addressing multidrug-resistant infections.

Despite the significant progress in nanoparticle research, challenges remain, including issues related to safety, scalability, and regulatory approval. Continued interdisciplinary collaboration between scientists, healthcare professionals, and regulatory bodies is essential to optimize the design and application of nanoparticles for clinical use. By addressing these challenges, nanotechnology has the potential to revolutionize the treatment of resistant bacterial infections, reduce the global burden of antimicrobial resistance, and safeguard the future of effective infectious disease management.

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Abbreviations

Ag	silver
AMR	antimicrobial resistance
AgNPs	silver nanoparticles
Au	gold
AuNPs	gold nanoparticles
CDC	Centers for Disease Control
CNTs	carbon nanotubes
CU	copper
CRISPR	clustered regularly interspaced short palindromic repeats
DCs	dendritic cells
DNA	deoxyribonucleic acid
EPS	extracellular polymeric substance
ESBL	extended-spectrum beta-lactamases
Fe ₂ O ₃	hematite
FDA	Food and Drug Administration
GQDs	graphene quantum dots
GMPs	Good Manufacturing Practices
GO	graphene oxide
GLPs	Good Laboratory Practices
ICD	immunogenic cell death
LHNPs	liposome-templated hydrogel nanoparticles
LNPs	lipid nanoparticles
LNLS	lipid nanostructured lipid systems
MBLs	metallo-beta-lactamases
MDR	multidrug resistance
MIC	minimum inhibitory concentration
MOFs	metal–organic frameworks
MRI	magnetic resonance imaging

MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MSNs	mesoporous silica nanoparticles
NCTR	National Center for Toxicological Research
NM	nanometers
NMDs	nanomedical devices
NPs	nanoparticles
PaβN	β-naphthylamide
PBPs	penicillin-binding proteins
PDA	polydopamine
PEG	polyethylene glycol
PEI	polyethyleneimine
PCL	polycaprolactone
PLGA	poly-lactic-co-glycolic acid
QS	quorum sensing
QSIs	quorum sensing inhibitors
RNA	ribonucleic acid
ROS	reactive oxygen species
SeNPs	selenium nanoparticles
SLNs	solid lipid nanoparticles
SORT	selective organ targeting
SPR	surface plasmon resonance
TiO ₂ NPs	titanium dioxide nanoparticles
UV	ultraviolet
WHO	World Health organization
ZN	zinc
ZnO NPs	zinc oxide nanoparticles

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