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REVIEW

Nanomedicine in the Fight Against Multidrug-Resistant Infections: A Review on Emerging Strategies and Translational Prospects

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Abstract: The global rise of multidrug-resistant (MDR) bacteria has rendered numerous traditional antibiotics ineffective, posing a major threat to public health. Nanomedicine has emerged as a promising multidisciplinary strategy to address these challenges by employing engineered nanomaterials such as liposomes, metallic nanoparticles, polymeric nanoparticles, dendrimers, and carbon-based nanostructures for targeted drug delivery and enhanced antimicrobial therapy. These nanomaterials possess unique attributes, including the ability to disrupt microbial cell membranes, generate reactive oxygen species (ROS), and facilitate controlled and site-specific release of antibiotics, which collectively increase the efficacy against resistant strains such as *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Klebsiella pneumoniae*. Beyond therapeutic applications, nanomedicine-based diagnostic platforms including magnetic nanoparticles, biosensors, quantum dots (QDs), and graphene-based transistors enable rapid and sensitive detection of MDR pathogens and resistance genes, facilitating timely intervention and personalized treatment approaches in resource-limited settings. Despite these advances, significant challenges remain in the clinical translation of nanomedicine, including issues of biocompatibility, toxicity, cost-effectiveness, regulatory approval, and large-scale manufacturing. Additionally, the potential for resistance development against certain nanomaterials warrants careful monitoring and continued innovation. Future perspectives focus on integrating nanotechnology with artificial intelligence (AI) to develop highly effective, adaptive, and personalized diagnostic and therapeutic modalities for MDR infections. Overall, nanomedicine holds considerable promise in combating multidrug-resistant microorganisms, reducing the global disease burden, and shaping the next generation of infection management strategies.

Keywords: nanotechnology, alternative treatment, antibacterial effects, dendrimers, liposomes, metallic nanoparticles

Introduction

Antibiotics revolutionized modern medicine by treating various bacterial infections and decreasing morbidity and mortality rates. Despite these advantages, the overuse of antibiotics leads to the development of multidrug resistance (MDR) in bacterial species, particularly the ESKAPE pathogens, including *Enterococcus faecium (E. faecium), Staphylococcus aureus (S. aureus), Klebsiella pneumoniae (K. pneumoniae), Acinetobacter baumannii (A. baumannii), Pseudomonas aeruginosa (P. aeruginosa)*, and *Enterobacter* species, which are resistant to lipopeptides, oxazolidinones, macrolides, tetracyclines, fluoroquinolones, β-lactams, polymyxins, a combination of β-lactam-β-lactamase inhibitor, carbapenems, and glycopeptides.[1] The most critical pathogens globally that need to be combated with the more advanced antibiotics are *P. aeruginosa, Enterobacter* species, and *A. baumannii*, as these bacterial species are resistant to the last-line drug for multidrug-resistant bacteria, ie, carbapenem.[2] The World Health Organization (WHO) states that the development of multidrug-resistant infections leads to a serious challenge to treatment methods, and affects global health, economy, and food security.[3] The consequences of multidrug-resistant pathogens are given in Figure 1.

Therefore, there is an urgent need to develop more effective treatment modalities for MDR infections, as current antibiotics are often rendered ineffective against these rapidly evolving pathogens.[4] The therapeutic challenge posed by

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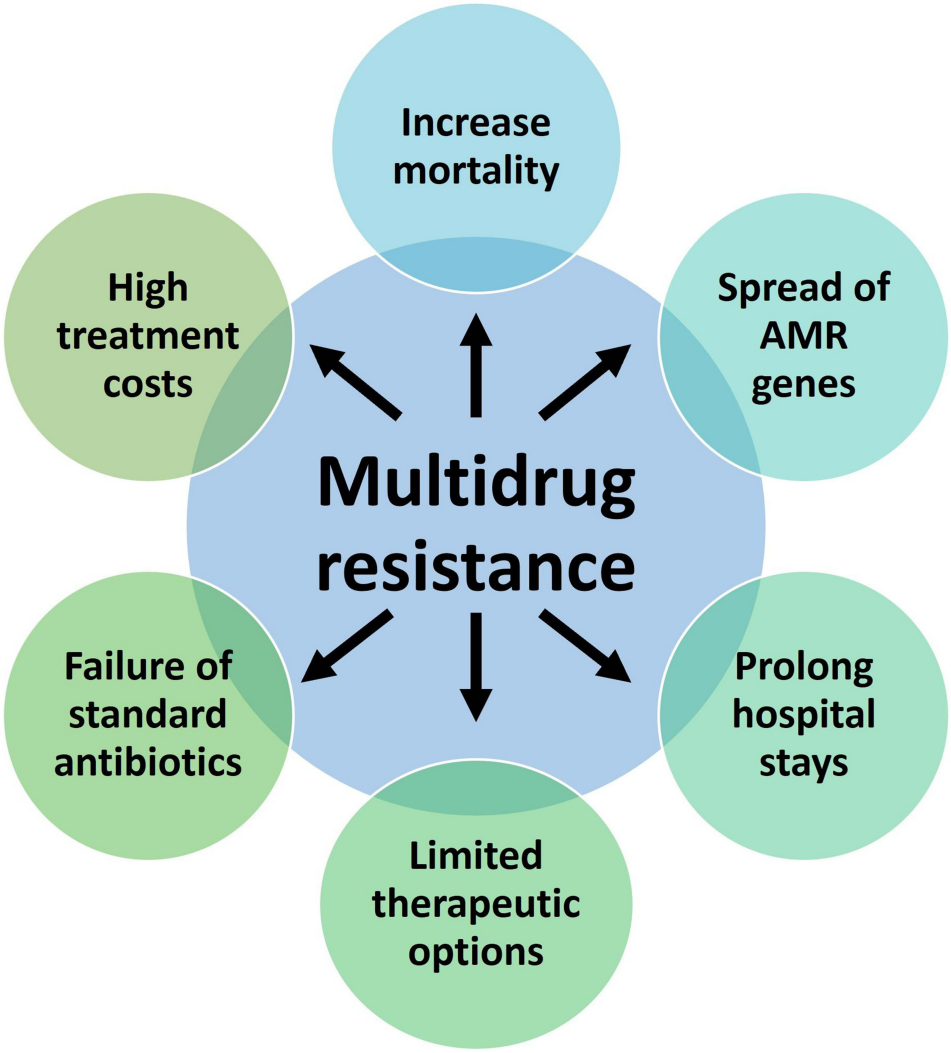

Figure 1 Associated outcomes of Multidrug resistance. Multidrug resistance can result in decrease in the efficacy of treatment, increase the risk of mortality rate, increase the treatment costs, prolong hospital stays, prolong illness. It rapidly develops in immunocompromised patients, and can lead to limited treatment options.
Abbreviation: AMR, Antimicrobial resistance.

MDR bacteria including ESKAPE pathogen demands innovative solutions to restore and enhance antimicrobial efficacy.[5,6] In parallel with new treatment strategies, improving early detection and prevention methods remains critical for limiting the spread of resistance and enabling timely clinical intervention.[7] Among emerging approaches, nanomedicine stands out as a versatile and promising avenue, offering targeted drug delivery, the ability to circumvent established resistance mechanisms, and the potential to simultaneously enhance both therapy and diagnostics for infectious diseases.[8–11]Nanoparticles are engineered, minute structures of a size range 1–100 nm, and are used as sensors, drug carriers, and antimicrobial particles that deal with AMR (Antimicrobial resistance) and even with bacterial biofilms. Nanoparticles is beneficial due to its ability to sustain release, enhanced penetration, targeted delivery, and enhanced solubility as compared to conventional therapeutic methods.[12] Nanomedicine with intrinsic attributes, ie, to enhance the effectiveness of traditional antibiotics, is also available to deal with MDR bacteria. The nanoparticles are used as carriers for antimicrobial therapies, such as in the form of polymeric nanoparticles, dendrimers, and liposomes, collectively termed Nanobiotics,[13] as well as used as an inherent therapy, such as zinc oxide (ZnO), titanium dioxide, nickel nanoparticles,[14] copper nanoparticles, silver nanoparticles, and selenium nanoparticles.[15] The carriers such as polymeric nanoparticles, liposomes, or dendrimer, are nanoscale delivery vehicles engineered to encapsulate and transport therapeutic agents (including antibiotics or peptides) directly to target sites of infection, thereby improving

drug bioavailability, enhancing cellular uptake, and enabling precise targeting of pathogenic microorganisms.[16–19] All of these nanoparticles have unique features that interact with the membrane components of bacterial cells, disturb biofilm, produce ROS (reactive oxygen species), and deliver antimicrobial agents with accuracy to the target.[20]

While nanoscale carriers such as polymeric nanoparticles, liposomes, and dendrimers are engineered to improve bioavailability and enable targeted delivery, not all nanoparticles inherently possess accuracy in tissue targeting. In practice, most nanoparticles administered systemically distribute throughout the body in a relatively conventional manner, with only a small fraction reaching the intended site due to biological barriers and clearance mechanisms. Achieving precise targeting requires additional modifications such as decorating the nanoparticle surface with specific ligands or optimizing particle size and surface characteristics to facilitate accumulation and uptake at the target cells or tissue.[21–23] Even with such engineering, the efficiency of targeted delivery is often limited in clinical settings, representing a significant challenge for the translation of nanoparticle-based therapeutics.

Apart from therapeutic applications, nanoparticles increasingly play a central role in diagnostics, enabling the rapid identification of microbial pathogens and the detection of genetic determinants conferring antimicrobial resistance. Nanomedicine-based imaging techniques and biosensors allow for highly sensitive and specific molecular detection of resistance genes such as extended-spectrum β-lactamase (ESBL) genes, carbapenemase enzymes, and other genetic markers thus supporting targeted and effective treatment strategies.[24–26] These diagnostic innovations are especially valuable in resource-limited healthcare settings, where rapid and accurate identification of resistant infections can improve patient outcomes.[25,27] While nanomedicine-based diagnostics and therapeutics offer rapid, sensitive, and innovative approaches for managing multidrug-resistant infections, it is important to acknowledge that the majority of advanced nanoparticle technologies are currently costly to produce and require considerable technical infrastructure. As a result, their implementation has been largely limited to well-resourced healthcare systems, and widespread adoption in low-resource settings remains more aspirational than routinely achieved.[12,28–30] Promising developments such as point-of-care (POC) nanodiagnostics, lab-on-chip devices, and microfluidic biosensors, are actively being optimized for affordability, simplicity, and robust function in resource-limited environments.[31–33] Some nanoparticle-enabled POC platforms have already improved access to rapid diagnostics in remote or underserved regions by reducing reliance on centralized laboratories and facilitating earlier intervention.[31,32]

Despite these advances, the widespread implementation of nanoparticle-based diagnostics and therapeutics faces significant challenges. These include high production costs, technical complexities in maintenance, variability in batch-to-batch reproducibility, and stringent requirements for quality control.[12,31–33] Furthermore, issues such as biocompatibility, potential toxicity, regulatory hurdles, and the demands of large-scale manufacturing continue to pose barriers to clinical translation and equitable deployment.[29,34–36] Although the risk of resistance development to nanomedicine is currently perceived to be low, it remains an important consideration for long-term effectiveness. Therefore, while nanotechnology holds substantial promise for improving equity in infectious disease diagnosis and management worldwide, realizing its full clinical potential will require sustained innovation focused on cost-effectiveness, scalable production, rigorous regulatory approval, and practical application in diverse healthcare settings. This review provides a comprehensive overview of nanomedicine strategies aimed at combating multidrug-resistant infections.

Review Methodology

This narrative review was conducted following principles based on the PRISMA guidelines for systematic reviews.[37] We systematically searched databases including PubMed, Scopus, and Web of Science using the keywords: “nanomedicine”, “antimicrobial resistance”, “multidrug-resistant infections”, “nano-enabled therapy” and “translational prospects”.

The search interval was until April 2025 (inclusive), covering major publications from the last years. Only peer-reviewed articles in English were considered. Inclusion criteria were:

- Original research or reviews addressing nanomedicine strategies for multidrug-resistant bacterial/fungal/viral infections
- Articles presenting translational, clinical, or preclinical data
- Studies reporting on diagnostics, drug delivery, or mechanistic insights

Exclusion criteria were editorials, conference abstracts, and non-English publications.

Two authors independently screened initial search results for relevance and quality. Disagreements were resolved through team consensus.

Types of Nanomaterials in Antimicrobial Therapy

Nanomaterials have diverse physicochemical attributes that make them well-adapted for their use as antimicrobial agents. They have a surface charge, tunable size, functionalization potential, and a high surface area to volume ratio, making them capable of more precise interaction with the microbes, enhancing their therapeutic efficacy and solubility. Diverse types of nanoparticles are studied for their effects against multidrug-resistant microbes; each of them has specific functions in diagnostics and therapeutics.

Liposomes

The field of nanomedicine builds upon several decades of foundational research into nanomaterial synthesis, functionalization, and biological interaction. For example, early clinical adaptation of liposomal drug delivery systems such as liposomal amphotericin B (AmBisome) and liposomal doxorubicin (Doxil) highlighted the value of phospholipid vesicles for improving therapeutic efficacy and reducing toxicity in infectious disease and cancer management.[38,39] Seminal work by Gregoriadis and Ryman first demonstrated the potential of liposomes for drug encapsulation and sustained release.[40] In the context of antimicrobial resistance, classic studies showed that liposome-encapsulated antibiotics could target resistant strains more efficiently than free drugs.[41–43]

Liposomes are composed of a phospholipid bilayer in spherical form, and this bilayer encloses an aqueous core. They are biocompatible, biodegradable, and can encapsulate hydrophobic and hydrophilic drugs and act as a vehicle to carry antimicrobials. Liposomes enhance the antibiotics' bioavailability, pharmacokinetics, precise delivery to the infection point, and reduce toxicity.[44] An example of liposome-directed drug delivery is Doxil, in which doxorubicin is loaded via a PEGylated liposome. Passive targeting was employed to deliver the drug, and it relies on EPR (enhanced permeability and retention).[45,46]

Liposomes have better permeability, as evidenced by the gentamicin and vancomycin in liposomal formulations, which exhibit enhanced permeability and efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa*, allowing for sustained penetration into tissues and release of the drug. Surface modifications of liposomes, like ligand conjugation and PEGylation, facilitate active and passive targeting of liposomes to the infection site with accuracy and increase therapeutic effects.[47]

Polymeric Nanoparticles (PNPs)

These nanoparticles can be synthesized from natural as well as synthetic polymers. The natural polymers include alginate and chitosan, and synthetic polymers include polycaprolactone (PCL) and poly lactic-co-glycolic acid (PLGA).[48] These nanoparticles ensure drug release in a very controlled manner and can deliver therapeutic agents by protecting them from the degradation of enzymes, and it is also known for delivering multiple drugs at the same time.[49]

Natural polymers such as chitosan and alginate are commonly used to prepare polymeric NPs. Chitosan, for instance, is recognized for its high biocompatibility, biodegradability, and inherent antimicrobial activity due to its cationic properties.[50–54] The chitosan have a cationic nature, due to which they have the ability to interact strongly with negatively charged bacterial membranes, leading to membrane disruption and antibacterial effects.[49–51] These features enable chitosan NPs However, while natural polymer-based NPs offer bioactivity, they may also demonstrate higher immunogenicity and batch-to-batch variability, potentially limiting their reproducibility and scalability in clinical settings.[50–54]

By contrast, synthetic polymeric nanoparticles, formulated from PLGA, PCL, Polylactic acid (PLA), Polyvinyl alcohol (PVA), or Polyethylene glycol (PEG), are deliberately engineered to offer predictable degradation, lower immunogenicity, and finely tuned drug release profiles, which enhance their translational potential for clinical applications.[52–56] Synthetic PNPs typically lack bioactivity unless specifically modified with targeting ligands, surface functionalities, or loaded agents, which can be tailored for specific therapeutic needs. Furthermore, the internal structure of PNPs, nanospheres (solid matrices) and nanocapsules (core-shell systems), directly affects drug encapsulation,

stability, and release kinetics, thereby influencing efficacy and safety in biomedical settings.[52–56]A few antibiotics like rifampicin and ciprofloxacin are encapsulated by nanoparticles composed of PLGA, which increases the efficacy of these antibiotics for intracellular microbes like *M. tuberculosis* (*Mycobacterium tuberculosis)*.[57] The functionalization of these nanoparticles with different ligands like peptides and antibodies promotes their delivery to particular tissues or the bacterial strain.[58]

Rigorous characterization of polymer composition, particle size, surface charge, and morphology, using techniques such as dynamic light scattering, electron microscopy, and zeta potential analysis, is critical to ensure reproducibility, performance consistency, and safety in drug delivery and other biomedical uses.[52–54,56] These nuanced differences between natural and synthetic polymeric nanoparticles highlight the importance of careful material selection and engineering for specific clinical applications.

3.3 Metallic and oxide nanoparticles Metallic nanoparticles, such as gold, silver, and copper nanoparticles, are intentionally synthesized nanoscale materials (1–100nm) known for their unique physicochemical, electronic, and catalytic properties. These engineered metallic nanoparticles exhibit pronounced antimicrobial activity against a wide spectrum of multidrug-resistant bacteria, including both Gram-positive and Gram-negative strains,[59] through mechanisms such as membrane disruption, induction of ROS, and inhibition of microbial metabolic pathways.[36,60–62] In addition to metallic forms, metal oxide nanoparticles including ZnO, copper oxide (CuO), and iron oxide (Fe_2O_3) nanoparticles, have emerged as potent antimicrobial agents. Their bactericidal effects are attributed to their ability to generate ROS, release metal ions, and physically interact with bacterial membranes, ultimately disrupting cellular integrity and function.[63–68]

Oxide nanoparticles, such as ZnO, have demonstrated broad-spectrum efficacy, with studies showing strong antimicrobial activity against both Gram-positive (eg, *S. aureus, Bacillus subtilis*) and Gram-negative (eg, *E. coli, P. aeruginosa*) pathogens.[63,65] The antimicrobial action is size-dependent, with smaller particle sizes generally exhibiting greater bactericidal potency due to higher surface reactivity. The development and biomedical application of both metallic and metal oxide nanoparticles represent important advances in the fight against multidrug-resistant infections.

Gold Nanoparticles (AuNPs)

Due to the inert nature of this metal, the AuNPs perform their function in the functionalization with peptides, antibiotics, and ligands. They are involved in the delivery of different drugs and are used most effectively for diagnostic purposes due to the unique optical attributes of this metal.[69]

AuNPs exist in various forms, distinguished by their size, shape, surface functionalization, and composition, each imparting unique biological activities and limitations.[60,70]

The most common types include spherical colloidal AuNPs, nanorods, nanocages, nanostars, and core-shell structures, which are synthesized for specific biomedical applications ranging from imaging to drug delivery and photothermal therapy.[70,71] For the treatment of chronic infections, AuNPs are used as cargo for the transport of dual therapeutic compounds having anti-inflammatory and antimicrobial properties. The surface of these nanoparticles is conjugated with dexamethasone, which is an anti-inflammatory compound used to prevent tissue damage. These nanoparticles have the potential to treat the infection of intracellular pathogens like *M. tuberculosis*.[72]

Spherical AuNPs are widely used for their simplicity and stable optical properties. Nanorods and nanostars are engineered for enhanced plasmonic effects suitable for diagnostic sensors and cancer therapy due to their tunable absorption in the near-infrared range.[70,71,73]

AuNPs generally exhibit high biocompatibility and low immunogenicity compared to other metallic nanoparticles, but their surface chemistry, especially when modified with biomolecules or polymer, can influence immune responses and cellular uptake.[73,74]

For example, AuNPs conjugated with antibodies and antigens have been shown to both amplify and modulate immune reactions, highlighting their potential as vaccine carriers or diagnostic adjuvants, but also indicating a need for careful immunological assessment.[71,73,74]

Limitations of AuNPs include size-dependent cytotoxicity, unwanted accumulation in tissues, and possible oxidative stress at very small diameters (<2 nm), necessitating comprehensive biocompatibility and safety evaluations prior to clinical application.[70,74]

Despite their relatively inert and stable nature, gold nanoparticles may still cause cell toxicity if used at high concentrations or with inappropriate surface ligands, and standardization challenges remain in regulatory frameworks for their safe biomedical deployment.[74,75]

Furthermore, AuNP-based nanocomposites and hybrid structures such as AuNPs loaded with drugs, peptides, or genetic material, can be tailored to enhance targeted therapy or bioactivity, but may inherit limitations or safety concerns from the combined materials.[70,73] Overall, the selection and engineering of specific types of AuNPs must be guided by a balance between desired bioactivity, minimal immunogenicity, optimal biocompatibility, and application-specific limitations.[70,74,75]

Zinc Oxide Nanoparticles (ZnO NPs)

The ZnO NPs exist in various forms, each exhibiting distinct physicochemical properties and biomedical characteristics depending on synthesis routes, particle size, surface charge, and functionalization. ZnO NPs can be synthesized by chemical methods (such as sol-gel and precipitation techniques) or by green methods using plant extracts or biopolymers. Chemically produced ZnO NPs typically possess smaller crystallite sizes, while green-synthesized ZnO NPs tend to have higher crystallinity and purity.[76–79]

The bioactivity of ZnO nanoparticles is closely linked to their ability to generate ROS, which underpins their prominent antibacterial, antifungal, antineoplastic, wound healing, and biosensor functions. These nanoparticles have photocatalytic activity, as the ROS increase when exposed to light. They are involved in the degradation of bacteria's biofilms using oxidative stress.[80]

Smaller ZnO NPs and those with positive surface charges show heightened cellular internalization and antibacterial effectiveness but may also display increased cytotoxicity when compared to their larger or negatively charged counterparts. ZnO nanoparticles are used for gram-positive as well as gram-negative bacteria like *S. aureus, P. aeruginosa*, and *E. coli*. As they show photocatalytic activity under ultraviolet, they are a potential agent for coating on food packaging and medical types of equipment. They are biocompatible, low-cost, and scalable agents for the management of antimicrobial-resistant infections.[81]

Immunogenicity and toxicity of ZnO NPs are variable and depend on several factors. ZnO NPs with different sizes and charges have demonstrated a range of immunotoxic effects, including induction of inflammation, suppression of natural killer cell activity, and alterations to cytokine profiles, sometimes leading to immunosuppression in vivo. Specific studies have reported oxidative stress, cytotoxicity, DNA damage, and organ inflammation (lung, liver, kidney, heart, and brain), which are concerns for clinical translation.[82–84] The surface charge is especially critical: positively charged ZnO NPs have shown higher cytotoxicity and enhanced cellular uptake than negatively charged NPs.[82–84]

Despite FDA approval of bulk zinc oxide as generally recognized as safe (GRAS), the nanoscale form poses unique toxicological risks due to high solubility and increased biological reactivity. These risks highlight limitations in clinical use, including potential pulmonary toxicity (by inhalation exposure), genotoxicity, and the need for careful dose selection.[82,83]

In summary, distinctions in synthesis approach, particle size, charge, and functionalization yield ZnO NPs with varying immunogenicity, bioactivity, and limitations, necessitating rigorous characterization and risk assessment for biomedical applications.[76–78,82–84]

Silver Nanoparticles (AgNPs)

The AgNPs are a diverse class of nanomaterials produced using various synthesis methods, including physical, chemical, and biological (green) routes, resulting in distinct particle sizes, shapes, and surface properties.[85–87] Each synthesis method can influence the immunogenicity, stability, and bioactivity profile of the resulting AgNPs; for instance, biologically synthesized AgNPs may have lower environmental toxicity and enhanced biocompatibility compared to those synthesized chemically.[85–88] The metallic nanoparticles are stable, and even their low concentration is effective, but there are a few concerns with regard to their biodistribution, cytotoxicity, and aggregation in tissues for the long term. The plant-based synthesis of these nanoparticles makes these particles biocompatible and with a lower cytotoxicity level.[89]

Silver nanoparticles have been investigated for their antimicrobial properties since the pioneering studies by Sondi and Salopek-Sondi in 2004, which demonstrated broad-spectrum bactericidal activity through membrane disruption and ROS generation.[90] Subsequent research study provided mechanistic insight into the size-dependent antimicrobial effects of silver nanoparticles.[91] AgNPs exhibit broad-spectrum antimicrobial activity against bacteria, fungi, and viruses through multiple mechanisms, primarily the release of silver ions (Ag+), generation of ROS, and disruption of microbial membranes.[85,92–94] They are used for coatings, and wound dressings, and are used along with antibiotics for the more enhanced synergic attributes.[95,96]

Their bioactivity is size-, shape-, surface charge-, concentration-, and time-dependent, with smaller sizes (<10 nm) showing enhanced antibacterial effects due to a higher surface-area-to-volume ratio. Spherical AgNPs have generally been observed to exhibit superior antibacterial efficacy compared to other shapes, highlighting the importance of morphology for bioactivity.[85,92–94]

However, one limitation includes potential cytotoxicity and immunogenicity. AgNPs may accumulate in tissues and cells, induce oxidative stress, and upregulate cellular markers related to inflammation and stress responses, which raises concerns for chronic or systemic exposure.[85,86,93,94] Moreover, long-term and improper use of AgNPs can induce microbial resistance through mechanisms such as increased expression of efflux pumps, biofilm formation, and genetic adaptation, including mutations allowing bacteria to detoxify or expel silver ions.[85,86,93,94]

Batch-to-batch variability in AgNPs, especially those synthesized using biological sources, can affect both biological activity and safety profiles, impacting scalability and reproducibility for biomedical use. Adjusting surface stabilizers, such as polyvinylpyrrolidone (PVP) or citrate, can help modulate immunogenicity and improve dispersion, but may also change bioactivity and biocompatibility.[85,87,88] Recent work has even described the development of novel sub-nanometer silver particles (silver Angstrom particles) which show better biological activity and lower toxicity compared to standard AgNPs.[85]

Dendrimers

Dendrimers are a class of highly branched, tree-like macromolecules that can be categorized by their core structure and surface functionality, leading to a range of biomedical properties.[97,98] Polyamidoamine (PAMAM) dendrimers are among the most widely studied, known for their regular architecture and ability to be tailored for drug encapsulation or conjugation, but higher-generation and cationic PAMAM dendrimers demonstrate increased cytotoxicity and immunogenicity compared to lower-generation or neutral/anionic types.[97,99] Polypropylene imine (PPI) dendrimers similarly offer versatile functionalization opportunities and substantial bioactivity, though their toxicity also correlates with generation and terminal group chemistry, requiring careful design for safe medical use.[97,100] Carbosilane dendrimers, featuring silicon-based backbones, have lower toxicity and immunogenicity than cationic PAMAM dendrimers, making them more suitable for biological applications.[97] Peptide dendrimers represent another type, engineered to enhance biocompatibility, and minimize the immune response, while maintaining functional versatility for gene delivery or antimicrobial use.[97,99]

Dendrimers were first explored as drug carriers, with applications for antimicrobial agent delivery soon following.[101–104] Early research in this domain revealed their potential for high drug loading and targeted release against resistant pathogens.[105] The bioactivity of dendrimers such as membrane penetration and targeted drug delivery, largely depends on their surface groups: cationic dendrimers can disrupt cell membranes via electrostatic interaction, leading to apoptosis, whereas anionic or neutral terminal groups decrease cytotoxicity and immunogenicity.[97,99,106,107] Despite their promise, limitations of dendrimers include cytotoxicity (particularly for cationic types), potential immunogenicity, restricted permeability for higher generations, and complex or costly synthesis and purification procedures. Many biomedical dendrimers are modified to balance activity with safety, such as PEGylation to improve solubility and circulation or surface neutralization to reduce immunogenicity.[97,99,106,107].

Rigorous assessment of dendrimer type, generation, and functionalization is critical to optimize biocompatibility, minimize side effects, and ensure reproducibility for diagnostic or therapeutic use.[97,99,107]

Furthermore, the engineering of dendrimers can improve the bioavailability of insoluble drugs as well as solubilize these drugs. These particles are engineered to respond to external stimuli like pH or respond in the presence of a specific

enzyme, which makes their delivery targeted and multidrug-resistant infection treated more efficiently. However, a few concerns about high-generation dendrimers are about their complexity and toxicity, which limit their clinical usage.[108]

Carbon-Based Nanostructures

Various types of carbon-based nanostructures include fullerenes, carbon nanotubes (CNTs), graphene oxide (GO), reduced graphene oxide (rGO), graphene quantum dots (GQDs), carbon nanofibers, and carbon dots (CDs), each with distinct characteristics impacting their biomedical applications and antibacterial activity.[109–114] Their synthesis may rely on top-down processes (eg, exfoliation of graphite for graphene and GO) or bottom-up approaches (eg, vapor deposition or chemical synthesis for CNTs, fullerenes, and carbon dots). Chemical and physical functionalization through covalent attachment of functional groups, noncovalent interactions, heteroatom doping, and bioconjugation, can improve dispersibility, targeting capacity, drug loading, and biological compatibility.[110–115] The development of carbon-based nanomaterials, such as graphene oxide and carbon nanotubes, was marked by discoveries of their ability to disrupt microbial membranes and generate oxidative stress, as evidenced by the previous studies.[116,117]

The immunogenicity and cytotoxicity profiles of carbon-based nanostructures vary considerably with surface chemistry, particle size, and degree/type of functionalization.[110,115] Recent reviews indicate functionalization generally reduces immunogenicity compared to raw materials, makes nanoparticles more biocompatible, and can tailor bioactivity. However, aggregation, sharp edges (eg, GO sheets), and residual catalysts may contribute to immune activation or cytotoxicity and thus represent critical limitations in some biomedical contexts.[110,115]

Distinct antibacterial mechanisms are observed: for instance, direct contact between CNTs, GO, or fullerenes and the bacterial membrane can disrupt membrane structure, induce metabolic compromise, and provoke cell death. Mechanisms include oxidative stress resulting from ROS generation, mechanical disruption of membranes (especially for 2D structures like GO), and interference with energy metabolism or DNA activity.[109,110,114]

The size and surface charge of carbon-based nanostructures are key determinants of antibacterial efficacy.[110,113] Smaller particles generally have a larger surface-to-volume ratio, supporting enhanced interactions with bacteria; positively charged surfaces may bind vigorously to negatively charged bacterial membranes, boosting membrane disruption. A recent study showed that smaller carbon dots demonstrated superior antibacterial activity owing to efficient membrane interaction and ROS production.[110,113]

Carbon-based nanoplatforms may be constructed from different foundational materials pristine or functionalized carbon nanotubes, graphene oxide, fullerenes, nanodots, or hybrid composites, that influence their antibacterial mechanisms.[110,114,118,119] For example, CNTs generally act via physical piercing and cell aggregation, GO by oxidative stress and membrane slicing, fullerenes primarily via ROS generation and metabolic interference, and carbon dots by membrane interaction and photo-induced processes.[110,114,118,119]

The choice of carbon nanomaterial, its size, surface charge, functionalization, and hybridization all determine its antibacterial action, immunologic profile, and suitability for a given clinical setting.[110,113–115,119]

GO Nanostructures

The GO nanostructures encompass a variety of forms including nanosheets, quantum dots, nanoribbons, and hybrid composites such as GO decorated with metal nanoparticles or embedded in polymeric matrices. Each structure possesses distinct physical and chemical characteristics determined by synthesis methods such as chemical exfoliation, Hummers' method, or electrochemical approaches, which control the number of layers, lateral size, oxidation degree, and defect density, ultimately impacting antibacterial activity.[116,120–122] GO nanostructures can be further functionalized by covalent grafting, non-covalent adsorption, and conjugation with metals (eg, silver, nickel, copper), polymers, and biomolecules, modifying their dispersibility, targeting, and biological interactions.[116,120–122]

These functionalization strategies not only optimize the bioactivity and stability of GO but also directly influence immunogenicity, cytotoxicity, and overall safety profiles, determining feasibility for therapeutic applications.[116,120,123,124] However, the use of GO nanostructures faces certain limitations: natural variability in size and composition, possible aggregation, and challenges in reproducible large-scale manufacture and toxicity control, including potential induction of reactive oxygen species and inflammation.[116,120,123,124] The basic characteristics of GO such as sheet size (smaller sheets

may induce more oxidative stress and membrane disruption; larger sheets tend to physically trap bacteria), surface charge (typically negative, but can be modified), and oxidation level, all markedly affect antibacterial mechanisms and efficacy. Higher defect density and sharp edges can physically puncture bacterial membranes, while charge interactions facilitate wrapping or entrapment, which may be bacteriostatic or bactericidal depending on context.[116,120,123,124] These sheets, along with antibiotics, are used to kill multidrug-resistant bacteria.[125]

Different materials can be incorporated to assemble GO nanoplatforms, such as AgNPs, nickel colloidal clusters, and copper nanoparticles, which impart synergistic activity and extend the antibacterial spectrum against resistant pathogens.[116,121–124] Their mechanism of action often combines multiple pathways including membrane disruption by sharp nanosheets, ROS-induced oxidative stress, entrapment and metabolic interference, or metal ion release from the composite, tailored by the nature of each GO-based nanostructure. For example, functionalization with AgNPs enhances bactericidal potential via both physical and chemical means, whereas hybridization with polymers or biomolecules can reduce cytotoxicity and improve biocompatibility.[116,121–124]

Graphene oxide showed effective results against *K. pneumoniae* and MRSA. It is used for the creation of nanocomposites due to its synergistic effect along with other nanoparticles and antibiotics. Due to its dispersion ability in water and biocompatibility, it is used for drug delivery, to disrupt biofilms, and for wound dressings.[126]

CNTs Nanostructures

The CNT nanostructures include single-walled carbon nanotubes (SWCNTs), multi-walled carbon nanotubes (MWCNTs), and double-walled carbon nanotubes (DWCNTs), each with distinct structural characteristics and synthesis methods.[127–129] SWCNTs consist of a single graphene cylinder and are typically synthesized via chemical vapor deposition (CVD), laser ablation, or arc discharge, whereas MWCNTs have multiple concentric graphene cylinders and may be produced by CVD or nanocycle production techniques. Functionalization of CNTs, such as covalent attachment of biomolecules, polymers, or drugs to their surface, improves solubility, dispersion, and reduces cytotoxicity while enabling targeted antibacterial activity.[127–129]

CNTs have electrical conductivity and effective mechanical strength; they have a needle-shaped appearance that allows them to penetrate inside the bacterial membranes, causing leakage of cytoplasmic content and ultimately cell death. They can overcome efflux pumps and targeted delivery of antibiotics, both single-walled and multi-walled CNTs can show antimicrobial properties along with other metal ions. They act as the major component of biosensors and also carry drugs. The carbon nanotubes penetrate the membranes and disrupt the cellular processes.[130]

The immunogenicity and bioactivity of CNTs are closely linked to their surface chemistry, physical properties, and degree of functionalization.[128,129] While pristine CNTs have potent bioactivity, they may exhibit cytotoxicity and provoke inflammatory responses; functionalized CNTs, such as those with carboxyl (-COOH) or amine (-NH2) groups, tend to show reduced toxicity and improved biocompatibility.[128,129] Limitations commonly encountered include aggregation in biological media, oxidative stress induction, inflammation, and batch variability arising from differences in synthesis and surface characteristics.[128,129]

Basic physicochemical characteristics, notably diameter, length, and surface charge, substantially impact their antibacterial performance. SWCNTs with smaller diameters and higher surface areas typically display stronger antibacterial activity due to enhanced membrane interaction and disruption, acting as nano-darts that physically penetrate bacterial cell walls and induce leakage of intracellular content.[127,131,132] The length of CNTs also influences toxicity shorter tubes have greater density of open ends, increasing antimicrobial effects, while longer tubes tend to have lower bacterial toxicity. Surface charge governs electrostatic interactions with the negatively charged bacterial membranes, promoting cell adhesion, membrane potential reduction, and antibacterial potency.[127,131,132]

Various materials can be used to assemble carbon nanotube-based nanoplatforms, including pristine CNTs, polymer-CNT composites, metal-oxide-functionalized CNTs, and drug-conjugated CNTs. These platforms operate through mechanisms such as direct physical membrane disruption, generation of ROS, wrapping and entrapment of the microbes, and interference with metabolic pathways.[133,134] Metallic CNTs often display higher antibacterial activity than semiconducting ones, owing to differences in electron transfer and ROS generation. The antibacterial effect may also be further enhanced by light activation, which induces additional ROS in bacterial cells.[133,134] All these factors; CNT type,

synthesis/functionalization, physicochemical properties, and the selected platform material, contribute to the spectrum, potency, and safety profile of CNT-based antibacterial nanostructures.[127–129,132,134]

Fullerenes

There are several types of fullerenes, including the classical C60 (buckminsterfullerene), C70, endohedral fullerenes (fullerenes containing metal atoms or clusters inside the cage), and functionalized derivatives such as fullerols (hydroxylated fullerenes) and amino fullerenes.[135–137] The synthesis of fullerenes commonly involves arc discharge, laser ablation, or chemical vapor deposition; further chemical functionalization can be applied to alter solubility, add targeting ligands, or improve bioactivity, for example by adding amino, carboxyl, or hydroxyl groups.[135–137] Functionalization impacts immunogenicity, hydrophobicity, biocompatibility, and the ability to interact with biological systems, which in turn changes their antimicrobial and cytotoxic profiles.[135–137] Although fullerenes and their derivatives exhibit bioactivity, some forms may induce inflammatory responses or cytotoxicity depending on dose, surface chemistry, and aggregation, which are considered limitations for biomedical uses.[135–137]

Basic characteristics such as particle size and surface charge significantly impact antibacterial activity.[110,138,139] Smaller fullerenes possess larger surface areas, facilitating adsorption onto bacterial membranes and transport into cells, thus enhancing bactericidal effects. Cationic (positively charged) fullerene derivatives show greater efficacy against Gram-negative bacteria, which have negatively charged cell surfaces, due to strong electrostatic interactions that improve cell membrane disruption and bacterial death. In contrast, anionic or neutral fullerenes are often less effective for the same reason.[110,138,139]

The material and mechanism of action of fullerene-based nanoplatforms also vary. Pure fullerenes act primarily by generating ROS under irradiation, causing oxidative stress, membrane disruption, protein denaturation, and DNA damage in target bacteria.[110,135,138,140,141] Furthermore, the C60 nanoparticles were reported photodynamic and antioxidant properties. They have a complex cape cage-shaped structure with singlet oxygen and release ROS upon photoactivation. They are involved in killing microbes by oxidative stress and conjugated with antibiotics for targeted delivery.[142]

Water-soluble or peptide-conjugated fullerene derivatives can enhance photodynamic efficacy and target multiple bacterial species, including multidrug-resistant strains, via improved membrane interaction and ROS production. Cationic, amphiphilic, or metal-coordinated fullerene nanomaterials possess further antibacterial advantages, including disruption of bacterial energy metabolism and increased permeability to antibiotics.[110,135,138,140,141] The assembly of nanoplatforms using combinations of fullerenes and other materials such as metals, peptides, and polymers, can allow for synergistic antibacterial actions and broaden pathogen coverage.[110,135,138,140,141]

The main nanomaterials employed for the treatment of multidrug-resistant infection, along with their composition, mechanism of action, pros and cons, and currently used model, is shown in Table 1.

Different nanomaterials, along with their antimicrobial properties and mode of action, is demonstrated in Figure 2.

Table 1 Nanomaterials and Their Attributes

Type	Composition/ Structure	Mechanism of Action	Pros	Cons	Models	References
Liposomal NPs	Phospholipids	Drug delivery by membrane fusion	Versatile drug loading; improved biocompatibility, controlled release	Short half-life, Stable, cost of formulation	Gentamicin, Liposomal vancomycin,	[17, 44]
Polymeric NPs	PLGA, chitosan	Membrane disruption, targeted release	Functionalization, customizable structure, controlled drug release, tunable degradation	Immunogenicity, production scaleup challenges	Chitosan nanoparticles, PLGA-ciprofloxacin NPs	[49, 52, 53, 143, 144]

(*Continued*)

Table 1 (Continued).

Type	Composition/ Structure	Mechanism of Action	Pros	Cons	Models	References
Metallic NPs	Silver particles	ROS generation, DNA or protein disruption	Broad-spectrum activity, rapid action	Cytotoxicity, environmental concern	AgNPs in wound dressings	[85, 92–95, 145–148]
	Gold cores	Photothermal therapy, Functional carrier	Stable and easy functionalization	Limited intrinsic antimicrobial activity, cost; potential accumulation.	AuNP–antibiotic conjugates	[60,70,71,73,147]
Metal Oxide NPs	ZnO nanostructures	Photocatalysis, ROS	Effective against biofilms and resistant strains; scalable	Dose-dependent cytotoxicity; bioaccumulation potential	ZnO antibiotic nanoformulations	[15,80–82,149]
Dendrimers	Branched polymers (PAMAM)	Drug delivery	High drug loading; surface modifiable	Synthesis and purification complexity; cytotoxicity (surface dependent),	PAMAM–antibiotic conjugates	[18, 97, 99]
Carbon-based NPs	Carbon structures	Cell membrane disruption by oxidative stress	Broad-spectrum activity, multifunctional	Potential cytotoxicity and immunogenicity; aggregation tendency	Graphene oxide, carbon nanotubes	[110, 115, 116]

Abbreviations: NPs, nanoparticles; PLGA, poly lactic-co-glycolic acid; AgNPs, silver nanoparticles, ROS, reactive oxygen species; AuNPs, gold nanoparticles; ZnO, Zinc oxide; ZnO NPs, Zinc Oxide Nanoparticles; PAMAM, Polyamidoamine.

Route of Administration: Local Vs Systemic Delivery of Nanoplatforms

The route of nanoplatform administration fundamentally influences the therapeutic efficacy and safety profile of treatments for infectious diseases, especially those caused by multidrug-resistant pathogens. Local application strategies such as topical gels

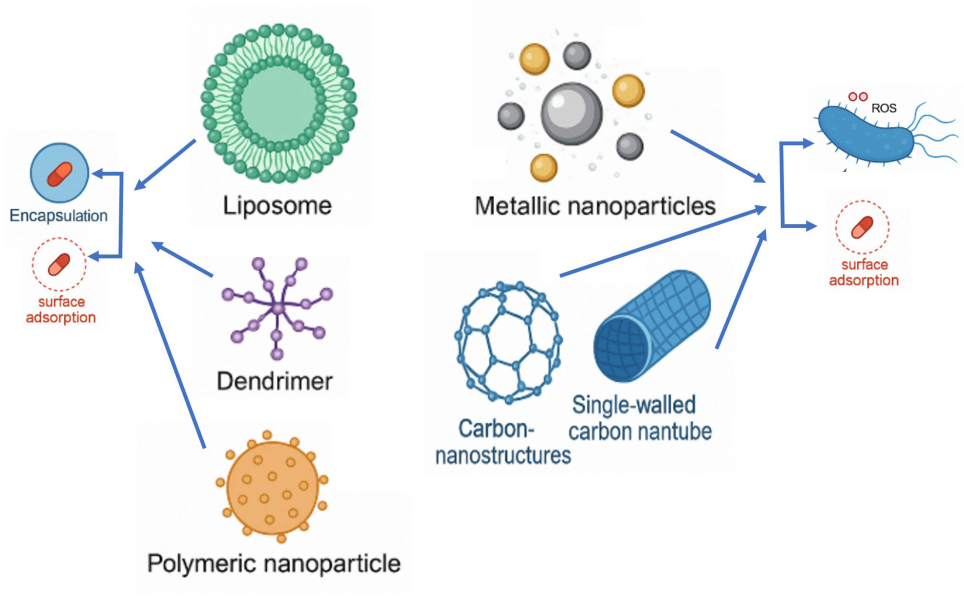

Figure 2 Different Nanomaterials and their antimicrobial properties.
Abbreviation: ROS, reactive oxygen species.

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for skin infections, wound dressings incorporating nanoparticles, inhalable aerosols for respiratory conditions, or intravaginal delivery for gynecologic infections, maximizing the concentration of active agents at the infection site. This targeted exposure enhances antimicrobial activity, limits systemic side effects, and reduces the risk of off-target tissue toxicity.[150–153] Moreover, localized delivery enables the use of higher drug doses, circumvents some mechanisms of systemic drug resistance, and has shown particular success in difficult-to-treat superficial or mucosal infections.[152,154]

In contrast, systemic administration including intravenous, oral, or intramuscular routes, is required for treating deep-seated, disseminated, or multi-organ infections where local application is impractical or ineffective. While systemic delivery allows therapeutic nanoplatforms to reach multiple or inaccessible sites, it is frequently challenged by biological barriers such as rapid clearance by the mononuclear phagocyte system, variable biodistribution, renal or hepatic elimination, and accumulation in non-target organs.[21,23,155,156] These factors can dilute drug concentration at the site of infection and elevate the risk of adverse effects. Achieving specific targeting and optimal drug levels in affected tissues therefore remains a major limitation for systemically administered nanomedicines.

Recent advances in nanoparticle engineering such as surface modification with ligands for enhanced targeting, stealth coatings (eg, PEGylation) to improve circulation time and evade immune clearance, and stimulus-responsive systems that release drugs in response to local microenvironmental cues, are actively under investigation to address these challenges.[154,156] The decision between local and systemic nanoplatform delivery should be individualized according to the infection's location, severity, patient-related factors, and properties of the nanomaterial, with ongoing research focused on improving both approaches.

Mechanism of Action

Nanomaterials are employed against MDR bacteria due to their ability to act through multiple antimicrobial mechanisms, providing a broader spectrum of activity than conventional antibiotics.[157,158] Unlike conventional antibiotics, which typically target bacteria via one or two specific biochemical pathways, nanomaterials exert their killing effect using a combination of biochemical, molecular, and physicochemical routes.[158,159]

This multi-modal action includes membrane disruption, generation of oxidative stress through ROS, intracellular penetration of antimicrobial agents, inhibition of biofilm formation, controlled release of therapeutic agents, and synergism with antibiotics.[157,160–162] Disruption of the bacterial membrane by nanoparticles may occur via direct interactions such as electrostatic attraction or adsorption of metal ions onto membrane components and can result in leakage, destabilization, and cell death.[161]

ROS generation by nanoparticles (such as silver, copper, zinc oxide, titanium dioxide) leads to oxidative damage of lipids, proteins, and DNA, further compromising bacterial viability and driving apoptosis or cell death.[160,161,163] Some nanoparticles penetrate into bacterial cells by diffusion or endocytosis, where they interact with intracellular targets including nucleic acids and enzyme systems, disrupting essential cell processes.[157,161] The ability of nanomaterials to inhibit biofilm formation is particularly valuable against MDR strains, as nanoparticles can disrupt established biofilms and prevent their regeneration by interfering with bacterial signaling and extracellular matrix components.[157,158]

Nanoparticles can act as drug carriers, enabling the controlled release of antimicrobial agents, which enhances efficacy and reduces the likelihood of resistance development.[158] Finally, combining nanomaterials with conventional antibiotics creates synergistic effects, increasing antimicrobial activity and bypassing resistance mechanisms that often thwart monotherapies.[157,158]

Microbial Membrane Disruption

One of the most common antimicrobial mechanisms employed by nanoplatforms is disruption of the bacterial cell membrane. Bacterial membranes are characteristically negatively charged due to the presence of teichoic acids in gram-positive bacteria and lipopolysaccharides in gram-negative strains, making them particularly vulnerable to positively charged (cationic) nanoparticles.[160,164,165] Cationic nanoparticles such as chitosan NPs, dendrimers, and metallic nanoparticles like ZnO and silver oxide are able to interact electrostatically with the bacterial membrane; these interactions lead to destabilization of membrane structure, increased permeability, and subsequent cell lysis with leakage of cellular contents.[160,164–166]

Experimental studies have demonstrated that chitosan-grafted oligolysine chains and branched polyethyleneimine-functionalized silver nanoclusters exert strong bactericidal activity by selectively binding to anionic bacterial membranes, causing membrane injury and cell death while sparing mammalian cells.[49,165,167–172] Mechanical disruption is another pathway: nanomaterials such as graphene oxide and carbon nanotubes physically interact with the bacterial membrane, sometimes piercing or rupturing the membrane and releasing cellular content, which directly damages the cell and reduces the risk of resistance development.[173–175]

Direct contact between nanoparticles and bacterial cell membranes has been identified as a primary mechanism for cytotoxicity; destructive interactions by carbon-based or inorganic engineered nanoparticles result not only from electrostatic attachment but also from physical tearing and oxidative or chemical stress.[145,175,176] Overall, these mechanisms, electrostatic disruption and mechanical damage, enable different nanomaterials to bypass traditional resistance pathways and exert powerful, multi-modal antimicrobial effects.[145,160,165,174,175]

Oxidative Stress by ROS

Metallic nanoparticles, such as ZnO nanoparticles, silver oxide nanoparticles, and titanium oxide nanoparticles, as well as carbon-based nanostructures, are known to possess photocatalytic properties that enable them to generate ROS.[177,178] The generation of ROS can occur spontaneously in biological environments or be stimulated by photocatalysis, leading to the formation of molecular species such as superoxide anion (O_2^-), hydroxyl radical, hydrogen peroxide, and singlet oxygen ($^1O_2$).[177,179] These highly ROS induce oxidative stress, which damages bacterial cells by disrupting essential biomolecules including proteins, lipids, and nucleic acids; this results in denaturation of proteins, lipid peroxidation of membranes, and degradation or fragmentation of bacterial DNA, rendering the microbes non-viable.[177,180]

The AgNPs, for instance, can bind to DNA and phosphorus-containing biomolecules, causing strand breaks and interfering with the replication process, ultimately leading to bacterial cell death.[177,181]

Furthermore, antibiotics delivered via nanoparticles can interact with the bacterial cell, inhibit the electron transport chain, interfere with efflux pumps, degrade crucial enzymes, destabilize ribosomal machinery, and inhibit protein synthesis, collectively leading to multifaceted disruption of bacterial viability, as shown in Figure 3.[177,182] Carbon-based nanoparticles like GO and fullerenes also produce ROS, especially upon photoactivation, which adds to their antimicrobial capabilities against targeted infections and biofilms, affecting bacterial survival and contributing to biofilm disruption.[177,183]

Molecular Targeting and Intracellular Penetration

Few nanoparticles can penetrate within cells by the process of passive diffusion or endocytosis, and it depends upon the charge, size, and hydrophobic nature of the particle. After internalization, these nanoparticles interact with the different targets inside the cell. The metallic nanoparticles, such as silver nanoparticles, interact with the DNA and disrupt the process of replication and transcription.[184] Few metallic and polymeric nanoparticles interact with the protein synthesis unit, ie, ribosomes and ribosomal RNA, disrupt other translation factors, and inhibit protein synthesis. The thiol group (-SH) containing nanoparticles interacts with the bacterial enzymes or inhibits the binding to the cofactor of the enzyme by replacing it, hence deactivating the enzyme activity as shown in Figure 4.[185]

The silver ion of the silver nanoparticle interferes with the function of the respiratory chain enzyme and reduces the production of adenosine triphosphate (ATP).[186] Nanoparticles are also involved in the disturbance of normal homeostasis of the cell by disrupting ion transportation through nanopore formation. These multiple strategies of nanoparticles make them an effective candidate for combating multidrug-resistant infections.[187]

Therapeutic Agents' Controlled Release

One of the most beneficial features of the nanoparticles is their capability to encapsulate antimicrobial drugs and release them in a very controlled manner at a specific target.[188] Different nanomaterials like liposomes, dendrimers, and polymeric nanoparticles like chitosan and PLGA are engineered to release the therapeutic drugs in response to specific cellular stimuli such as enzymes, pH, temperature, or some oxidation-reduction condition at the site of microbial infection.[189]

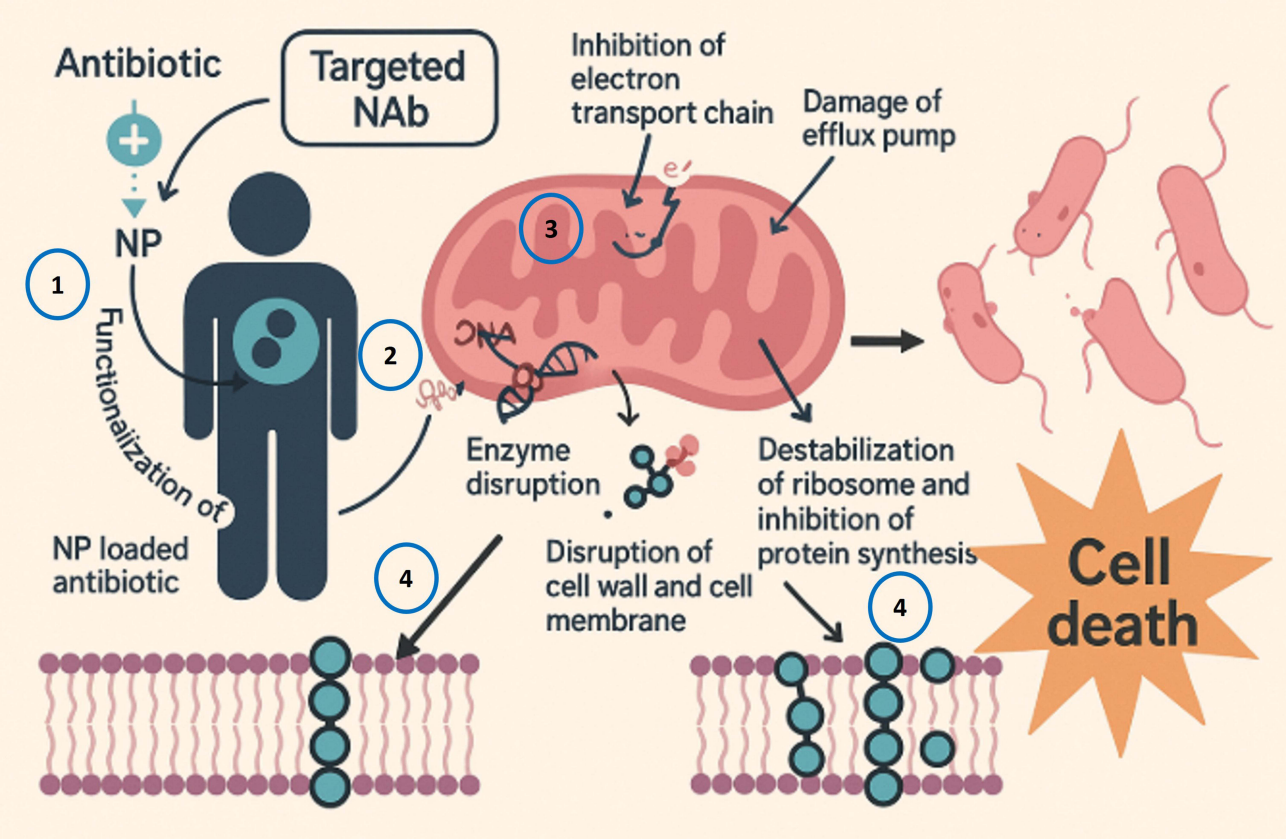

Figure 3 Nanoparticle (NP)-mediated antibiotic delivery and cell disruption using the oxidative stress mechanism. (1) Functionalized NPs encapsulate or conjugate antibiotics, ensuring enhanced stability and site-specific delivery to bacterial cells. (2) NPs attach to the bacterial cell wall and membrane, facilitating antibiotic entry and enhancing penetration. (3) NPs disrupt the cell wall, membrane, enzymes and mitochondria, destabilization of ribosomes and inhibition of protein synthesis, inhibit electron transport chain, damage efflux pumps, and generate reactive oxygen species to induce oxidative stress. (4) The synergistic mechanisms culminate in irreversible bacterial killing, offering a dual-therapeutic approach.
Abbreviations: NPs, nanoparticles; NAb, nanoparticle albumin bound.

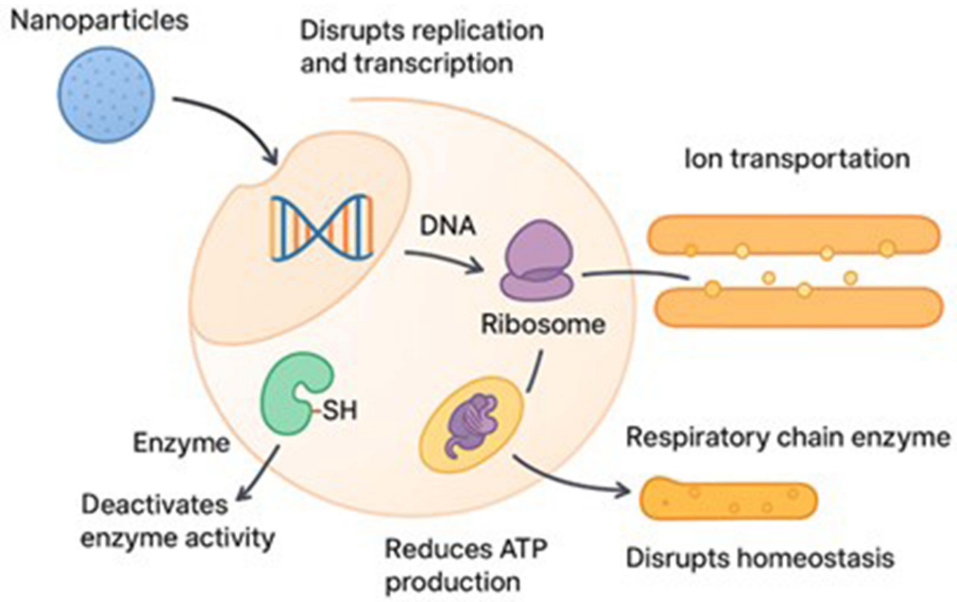

Figure 4 Penetration of silver nanoparticles to inhibit protein synthesis to combat multidrug resistant infections.

The active targeting of these nanoparticles is done by modifying the surface of nanoparticles with antibodies, and aptamers having some specific biomarkers or peptides. The passive targeting depends on the EPR effect, where some infected site allows the aggregation of these nanoparticles.[190] The targeted delivery has benefits like enhanced bioavailability, and reduced toxicity, and ensures the maximum concentration of the microbial agent at the targeted site.

Penetration of Biofilm

Biofilms are microbial cell communities aggregated in extracellular polymeric substance (EPS). It is very difficult to disrupt a biofilm as antibiotics are not capable of penetrating; also, the internal environment of the biofilm is altered, and slow-growing cells are present within this network.[191] Nanomaterials can penetrate these complex biofilms in several ways, such as by physical penetration into biofilms, as nanoparticles have a small size and can penetrate better than traditional antibiotics. Some engineered nanoparticles carry specific enzymes like proteases and DNases, or they may have the ability to generate ROS, which can degrade EPSs and make the individual bacteria susceptible.[192]

Few nanoparticles can interact with the cell signaling pathways, and these pathways are essential for the maintenance of biofilms.[193] The nanoparticles release the antimicrobials to the core of the biofilm, hence destroying it more effectively than traditional antibiotics. In *P. aeruginosa* and *S. aureus*, the biofilm formation is inhibited by chitosan and graphene oxide.[194]

Synergism with Traditional Antibiotics

Another important approach is the transport of traditional antibiotics with nanoparticles by engineering. This synergism of nanoparticles with traditional antibiotics enhances the efficacy of antimicrobial treatment. The nanoparticles disrupt the cell membrane and promote antibiotic uptake; they also protect the antibiotic from degradation, and they reverse the resistance mechanism by altering the target sites and by efflux pumps.[195]

Several studies supported the fact that antimicrobial activity is enhanced when antibiotics are transported via nanoparticles, like gold or silver nanoparticles and dendrimers. As in the case of vancomycin encapsulated with liposome and tetracycline in silver nanoparticles, it showed enhanced antimicrobial activity against MRSA and *E. coli*.[196] Tetracycline (and other antibiotics) creates a TET–AgNP complex that more strongly binds to *Salmonella typhimurium* (≈21% increased Ag binding) and enhances Ag+ release (≈26%), producing a local Ag+ burst at the cell envelope that disrupts cellular function and prevents growth as shown in Figure 5.

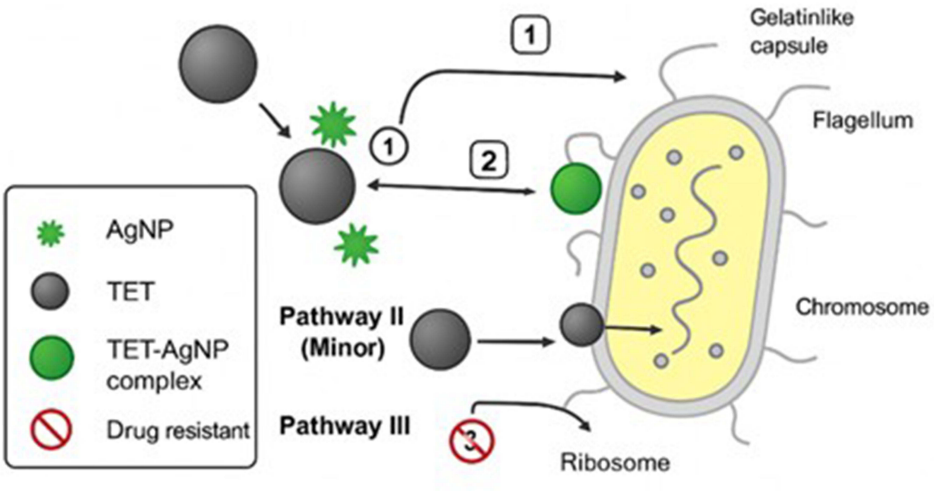

Figure 5 Synergism of silver nanoparticles with antibiotics to inhibit MDR *Salmonella typhimurium* DT 104. (1) Pathway I Direct attachment of AgNPs to the bacterial surface, leading to increased membrane binding and Ag+ ion release. (2) Pathway II (Minor): Formation of a TET–AgNP complex that penetrates the bacterial cell, interacting with intracellular targets and disrupting cellular processes. (3) Pathway III: Tetracycline molecules, either free or complexed, interact with ribosomes to inhibit protein synthesis, while AgNPs potentiate this effect by damaging the ribosomal machinery.

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Nanoparticles as Carriers for Antimicrobials

With the emergence of multidrug-resistant bacteria, there was a need to transport these antimicrobials to the infection site. Nanoparticles are engineered to act as a vehicle to transport these antimicrobial components.[197] These nanoparticles encapsulate, protect, and transport these antimicrobial components to the targeted site. These nanocarriers enhance therapeutic efficiency by improving stability, and solubility, and reducing the toxicity and degradation of antimicrobials. The two major strategies to transport the antimicrobials to the targeted site are active and passive targeting.[198] Nanoparticles also neutralize the toxicity caused by a few antibiotics, such as colistin, an antibiotic also has some nephrotoxic effects when given alone, but when colistin is encapsulated with liposomes, a reduction in nephrotoxicity was observed.[199]

Other nanomaterials like chitosan and dendrimers promote the penetration of the drug into bacterial cells, and targeted therapeutic effects can be achieved with relatively low concentrations of the drug.[200] The encapsulation of the antibiotics with nanocarriers protects the drug from degradation and improves the efficacy of the treatment. Nanocarriers are also employed for the combined therapies, as it is loaded with two or more drugs to find out the synergic polymeric effect against polymicrobial infections.[182] The nanocarriers overcome the traditional limitations, like toxicity, and also improve pharmacokinetics.[201]

Composite and Hybrid Nanomedicine Strategies

Composite and hybrid nanomedicine systems, characterized by the integration of two or more bioactive components such as antibiotics, peptides, metals, enzymes, and polymers into a single nano-platform, are transforming the management of MDR infections. By leveraging synergistic antibacterial actions, these platforms expand pathogen coverage and enable significant dosage reductions, thereby lowering toxicity and potentially slowing the emergence of resistance.[177,202]

Recent studies have demonstrated that combination nanoparticle platforms, such as silver–platinum (AgPt) nanohybrids, exert potent synergistic antibacterial and antibiofilm effects when paired with conventional antibiotics. For example, AgPt nanohybrids combined with streptomycin, rifampicin, or ampicillin have led to markedly reduced minimum inhibitory concentrations and improved biofilm eradication against *E. coli, S. aureus*, and *P. aeruginosa*.[203] These outcomes highlight the potential of metal–metal hybrid nanoparticles as adjuvants to conventional drugs.

Hybrid metallic nanoparticles conjugated with antibiotics or antimicrobial peptides have also been shown to surpass the efficacy of single-agent therapies, effectively suppressing MDR pathogen growth and preventing biofilm formation.[204,205] Polymeric nanogels and dendrimer-based composites designed to co-deliver multiple drugs or enzymes have demonstrated broad-spectrum activity against drug-resistant strains, disrupting established biofilms and improving antibiotic penetration.[206,207] Furthermore, composite nanomedicines that incorporate ZnO or CuO nanoparticles alongside antibiotics achieve deeper antibacterial action, including up to six-fold reductions in drug dosage, with significant efficacy against MDR *P. aeruginosa*.[208]

Hybrid nanosystems are increasingly being engineered for precision combination therapy, allowing either simultaneous or staged release of agents with complementary mechanisms of action. Examples include polymer–lipid hybrid nanoparticles loaded with antibiotics and antimicrobial peptides, as well as nanofiber membranes combining metallic nanoparticles with antibiotics for long-term barrier effects.[204,205] Such architecture not only enhances bactericidal synergy but can also improve local retention and support chronic infection management.

The mechanistic advantages of these composite strategies stem from their capacity to attack bacteria through multiple pathways including cell membrane disruption, metabolic interference, ROS generation, and efflux pump inhibition, making resistance emergence less likely.[202,209] The integrated delivery further improves pharmacokinetic profiles, reduces systemic toxicity, and enhances targeting of intracellular infections and biofilm-associated communities. As research advances, composite and hybrid nanosystems have the potential to become a cornerstone in the clinical management of MDR infections.

Nanomaterial-Based Diagnostics

To manage an infection, there is a need for an early and accurate diagnosis of a particular infection. Conventional culture-based detection methods are reliable but time-consuming and require more labor work. With the advancement of nanotechnology, the diagnostic methods have been revolutionized, as these techniques are considered to have point-of-care abilities making the diagnostic methods more reliable, fast, sensitive, and accurate.[210] Nanodiagnostics have all the physicochemical attributes of the nanoparticles, like tunable magnetic behavior, high surface area to volume ratio, and unique optical properties to identify pathogens with more accuracy and instantly. The AuNP have surface plasmon resonance, and these particles are being used in calorimetric assays. The AuNPs are engineered and tagged with antibodies and DNA/RNA probs, they can identify the DNA and RNA containing pathogens and antigens by visible color alteration, reducing the need for fancy instrumentation.[211] Multiplexed colorimetric and plasmonic biosensors based on AuNPs have been designed to rapidly detect multiple bacterial strains and distinguish between susceptible and resistant phenotypes. Functionalized AuNPs can bind specifically to target DNA or proteins such as the mecA gene of MRSA, enabling visual or electronic readouts for point-of-care diagnosis. Their versatility is demonstrated in the creation of lateral flow assays (LFAs) and surface-enhanced Raman scattering platforms that allow for multiplexed detection with high sensitivity and specificity.[212,213]

For the capturing of pathogens and biological specimen enrichment, magnetic nanoparticles (MNPs), are used. The particles are engineered to tag with ligands that interact with pathogenic cells, ensuring the separation of these pathogens by magnetic filtration before detection. These magnetic particles are integrated with biosensors to reduce the detection time. Such biosensor systems are used for the detection of *Salmonella, M. tuberculosis*, and *E. coli* in sputum and blood.[214] In addition, MNPs, especially iron oxide-based particles, offer rapid and efficient separation of bacterial DNA/RNA from complex clinical samples. MNPs are conjugated with capture probes or antibodies, facilitating targeted extraction of nucleic acids encoding resistance factors such as New Delhi metallo-β-lactamase-1 (blaNDM-1) and vancomycin resistance (vanA). Integrated with PCR, isothermal amplification, or microfluidic devices, magnetic nanoparticle platforms achieve quick turnaround times and enable downstream identification of MDR bacteria, providing reliable tools for surveillance and outbreak containment.[215–217] In multiplex pathogen detection, QDs are used, which are nanocrystal semiconductors and give fluorescence according to size. Their broad excitation spectra and higher photostability enable to detection of several pathogens simultaneously. It is usually used for the detection of hospital-based infections caused by MRSA and *P. aeruginosa*.[218]

Another diagnostic platform is Graphene-based field effect transistors (FETs). These sensors can detect the binding ligands with extraordinary sensitivity and in real-time. These are tagged with specific antibodies or aptamers, and they can identify RNA, bacterial toxins, and whole complete cells within a short time. It can detect a very low concentration of MRSA in wound specimens to 10 CFU/mL.[219] Furthermore, Graphene, with its large surface area and high electron mobility, is engineered into transistor-based biosensors capable of detecting nucleic acids (such as mecA, blaNDM-1, vanA) at extremely low concentrations critical for early diagnosis and monitoring. These devices enable rapid, label-free identification of MDR bacteria and can be integrated into portable or wearable technologies for real-time clinical decision support.[220,221]

Silver nanoparticles have been incorporated into electrochemical and optical biosensors for the rapid detection of bacterial pathogens. For example, AgNP-modified electrodes enhance the sensitivity of DNA hybridization sensors that target resistance genes in *E. coli* and *S. aureus*. Silver's strong plasmonic and antimicrobial properties also enable dual identification and viability assessment.[222–229]

Upconversion nanoparticles (UCNPs) add further versatility, providing dual-mode (luminescence and colorimetric) sensing capabilities. Conjugated with probes for resistance genes, UCNPs facilitate highly sensitive and instrument-free identification, which is essential for deployment in resource-limited settings.[230–232] Likewise, CNTs, often integrated into nanocomposite sensors with metals, supply electronic biosensors with ultra-sensitive, label-free detection capacity. Their high conductivity and surface area allow rapid identification of microbial markers, directly from clinical samples.[233,234]

Finally, hybrid platforms that combine magnetic beads with functionalized nanoparticles streamline laboratory workflows by enabling automated sample enrichment, nucleic acid extraction, and detection of resistance genes. These

magnetic nanoplatforms are especially valuable for high-throughput diagnostic pipelines, where speed and sample processing efficiency are critical.[213,215,235] Collectively, these complementary nanoparticle technologies form the backbone of next-generation diagnostic systems for multidrug-resistant infections. Their integration into clinical microbiology and molecular diagnostics promises a future of faster, more accurate, and multiplexed identification, supporting improved patient outcomes and better infection control.

Another diagnostic application of nanoparticles is LFAs. This method is commonly employed in pregnancy tests, and further advancement in nanobiotechnology enables the detection of bacteria with the help of nanoparticles. For instance, pathogens like *Streptococcus pneumoniae* (*S. pneumoniae)* and *Clostridium difficile* can be easily detected from respiratory and stool samples by using AuNPs-based lateral flow assays.[236] These assays are particularly useful in low-resource healthcare settings. Furthermore, there is a need to address challenges related to reproducibility, regulatory approval, and scalability, although these diagnostic methods are reliable, efficient, and rapidly diagnosed.

Furthermore, theranostic nanomaterials represent a major advance in the management of MDR infections, combining diagnostic and therapeutic functionalities within a single nanoplatform. These systems such as AuNPs, QDs, UCNPs, and multifunctional polymeric carriers are being engineered to simultaneously identify pathogens, monitor infection status, and administer targeted antimicrobial therapy. For example, gold nanorods conjugated with antibiotics have enabled rapid photoacoustic imaging of infection sites followed by heat-triggered drug release, while luminescent quantum-dot nanoassemblies facilitate both the swift detection of MDR bacteria and photodynamic microbial eradication. Lipid-based nano-formulations and magnetic nanoparticles can be functionalized for dual imaging and site-specific drug delivery, supporting real-time monitoring of treatment efficacy in vivo.[237,238]

Integration of diagnostic markers and therapeutics within theranostic nanoagents allows for precise infection targeting, dynamic assessment of therapeutic response, and minimized recurrence rates. These technologies increasingly incorporate stimuli-responsive functions such as light or pH-triggered drug release, providing tailored management of infections with complex resistance profiles. Recent reviews emphasize that rationally designed theranostic nanoplatforms can improve detection sensitivity, enhance pathogen eradication, and facilitate the translational progress of novel antimicrobial technologies against MDR bacteria and fungi. Collectively, theranostic strategies hold considerable promise for advancing personalized and precision medicine in infectious disease management.[237,238]

Mechanisms of Antimicrobial Resistance and the Advantages of Nanomedicine Approaches

The AMR arises through complex bacterial adaptation mechanisms, principally including drug target modification, enzymatic degradation or inactivation of antimicrobial agents, active efflux of drugs by membrane transporters, decreased membrane permeability, and robust biofilm formation.[239–241] These mechanisms are often triggered by repeated exposure to conventional antibiotics under conditions of strong selective pressure. Furthermore, bacteria frequently acquire and disseminate resistance genes through horizontal gene transfer mediated by plasmids, transposons, and bacteriophages, which accelerates the spread of resistance between different strains and even across species boundaries.[242,243] Nanoparticles offer fundamentally different and advantageous approaches to overcoming AMR due to their unique nanoscale size, high surface area-to-volume ratio, and customizable surface properties.[244,245] Unlike traditional antibiotics, which typically act via a single molecular target, nanomaterials exert multifactorial antibacterial actions: they can disrupt cell membranes physically, generate ROS that induce oxidative damage, interfere with bacterial metabolic pathways, suppress efflux pump activity, and penetrate biofilms that shield bacteria from conventional drugs.[16,161,246–249] Metallic nanoparticles such as silver and copper oxide have demonstrated the ability to maintain potent activity against a broad spectrum of microbes, with minimal resistance emergence even after repeated exposure.[250,251] Likewise, nanocarriers loaded with antimicrobial peptides or antibiotics enhance drug delivery to infection sites, improve pharmacokinetics, and allow for lower effective doses, further reducing the selective pressure that typically drives resistance.[150,252,253]

This multiplexed mechanism of action drastically diminishes the likelihood that bacteria will successfully evolve simultaneous resistance to all affected pathways, as opposed to the rapid adaptation observed with monotherapeutic

agents. Nevertheless, cautious monitoring and innovation are essential, as rare cases of bacterial adaptation to specific nanomaterials have been reported, although at a much lower frequency than with traditional antibiotics.[247,249] Overall, current evidence indicates that well-designed nanoparticles disrupt bacterial survival through multiple mechanisms, greatly impeding the development of lasting resistance. Sustained research and judicious clinical application will be crucial for maintaining efficacy against multidrug-resistant pathogens.

Current Progress in Nanoparticles to Combat AMR

With an increase in antimicrobial-resistant strains, nanotechnology has aimed to develop better therapeutics. In the last decade, the research on nanoparticles showed progress from laboratory-based research to preclinical and clinical trials, which showed potential outcomes in the treatment of multidrug-resistant infections. This progress is a multidisciplinary effort by microbiology, material science, and the engineering of nanoparticles, pharmaceutical engineering is on the list for the development of multifunctional nanoparticles.[254]

Many formulations of the nanoparticles showed their efficacy by overcoming various resistant mechanisms, such as disruption of biofilm, penetration of the membrane, and inhibition of the efflux pump. The silver nanoparticles are used for the treatment of various multidrug-resistant infections caused by pathogens like *E. coli, S. aureus, K. pneumoniae*. These nanoparticles use a multifaceted mode of action, like DNA binding and oxidative stress, to reduce the bacterial capability to develop resistance. The silver nanoparticles are formulated for wound dressing and are also being evaluated for burn infections and diabetic foot ulcers.[255]

Lipid-based nanoparticles, liposomes, encapsulate less soluble antibiotics like rifampicin and vancomycin to improve penetration into the tissues and bioavailability. Different liposomal formulations, like Arikayce, are used for the treatment of *Mycobacterium avium* complex (MAC), and it is an FDA-approved nanoparticle for the treatment of pulmonary infections. These formulations have the potential to deliver existing drugs and enhance their therapeutic effects.[256]

The biodegradable polymeric fabricated material, like PLGA, has been employed for targeted drug delivery, reducing the development of resistance, and reducing toxicity. These nanoparticles showed promising results in animal models. The nanoparticles are used as carriers for dual-functional drugs, along with biofilm-disrupting material or quorum-sensing inhibitors. The transport of these dual-functional drugs is currently under study, particularly for chronic wound infections and catheter-linked infections.[257]

The magnetic nanoparticles use physical means along with antibiotics to kill bacteria and other pathogens. These hybrid particles can destroy biofilms, which is not easy to disrupt by conventional medicines, however, these magnetic nanoparticles have been studied only under laboratory conditions, and no pre-clinical or clinical trials have been conducted yet. However, these nanoparticles may play a role in the treatment of multidrug-resistant infections by theranostics shortly.[258]

The small interfering RNA-loaded nanoparticles are another emerging nano-vaccine against the immune system of multidrug-resistant pathogens. The preclinical and in vitro trials have been started in which these nanoparticles carry siRNA or host-specific antigens to directly target the bacterial or pathogenic virulence factors or the resistance genes, therefore directly reducing the pathogenic load.[259] The nanoparticles for the treatment of multidrug infections, are under consideration, as listed in Table 2.

Challenges in Clinical Translation

The challenges in clinical translation are manufacturing limitations, regulatory uncertainty, and safety concerns. The biocompatibility and safety of nanomaterials are the major concerns. The nanoparticles may aggregate in vital organs like spleen, kidneys, and liver, causing inflammation, immunogenicity, and oxidative stress. The long-term certainty about the toxicity of many nanoparticles is not available, and regulatory cautions are needed for clinical usage.[260] Reproducibility and scalability are other hurdles. As the formulations of nanoparticles are reproducible in the Laboratory reproducing these results in industries is difficult. The standardization and quality control of these nanoparticles are needed. The regulatory guidelines for nanoparticles are not universal.[261]

The European Medicines Agency (EMA) and Food and Drug Administration (FDA) issued general guidelines, but they are adapted from conventional antibiotics. The specific guidelines for nanoparticle approval and usage are required.

Table 2 Clinical Trial Phase I of Nanoparticles for Treatment of Bacterial Infections

Nanoparticles	Country	Study Type	Bacteria/ Disease	Mechanism of Action	Condition	Intervention	Outcome	Status	Reference
PLGA	Egypt	Interventional	Enterococcus faecalis, Endodontic infections	Antibacterial nanoparticles were used because of their small size, sustained release and positive charge which interact with the negatively charged surface of bacterial cell causing its destruction.	Antibiotic Resistant Infection	Ciprofloxacin	Controlled release of the drug with associated with infection inhibition	Completed, Early Phase I	NCT05442736*
Ag	Brazil	Interventional	Streptococcus mutans, Dental Biofilms	Controlling the growth of S. mutans present in dental plaque of children.	Dental Caries	Fluoride	Evaluation of effectiveness of nanosilver fluoride on bacterial growth in the dental biofilm	Completed, Phase I	NCT01950546*
Au-Ag-Cu2O	China	Interventional	Drug-resistant Microbial Keratitis	Hollow gold and silver alloy cuprous oxide shell nano-shell hydrogel was excited by NIR laser to release functional silver ions, copper ions and ROS	Keratitis, Ulcerative, Antibiotic Resistance, Microbial, Photothermal Therapy	Hollow gold and silver alloy cuprous oxide shell nano-shell hydrogel, Voriconazole eye drops	Measurement of contact tonometry with iCare TA01i tonometer after treatment (1 day, 1 week, 1 month), Measurement of distance visual acuity with subjective refraction after treatment (1 week, 1 month)	Unknown status, Early Phase I	NCT05268718*

AgNPs	Saudi Arabia	Interventional	Inhibition growth of bacterial strains in the face or other parts of the body.	The active group will receive silver nanoparticles in different dosage forms as an anti-microbial drug.	Foot Infection Fungal, Infection, Bacterial	Topical approved anti-microbial gel	Stable topical anti-microbial silver nanoparticles, the antimicrobial activity of silver nanoparticles in the two groups of control and an infected patient will be determined.	Unknown, Early Phase 1	NCT03752424*
Nanoparticles containing Glutathione	United State	Interventional	Mycobacterium Infection	The therapeutic absorption of glutathione following topical Glutaryl application in increasing blood GSH levels without an invasive procedure.	Mycobacterium Infection	Glutaryl Solution, Placebo Solution	Demonstrate that increased levels of GSH in the experimental group is accompanied by decreased levels of ROS, demonstrate that increased levels of GSH in the experimental group is accompanied by altered levels of pro- and anti-inflammatory cytokines and chemokines,	Completed, phase 1	NCT05926245*

Note: *https://clinicaltrials.gov/.

Abbreviations: PLGA, poly lactic-co-glycolic acid; ROS, reactive oxygen species.

To develop nanoparticles and their formulations, a high cost is required, which discourages pharmaceutical companies is another hurdle.[262]

One of the major challenges in translating nanomedicine into clinical success is achieving efficient and selective delivery of nanoparticles to the intended site of infection or disease. Although nanoparticles are designed with the goal of targeted therapy, in practice, the majority of systemically administered nanoparticles undergo conventional biodistribution. Most particles are sequestered by the mononuclear phagocyte system, resulting in predominant accumulation within the liver, spleen, and other reticuloendothelial organs, rather than at the desired pathological site.[21,22] This nonspecific distribution limits therapeutic efficacy and may increase the risk of off-target effects.

To address these limitations, two principal strategies for nanoparticle targeting have been developed: passive and active targeting. Passive targeting exploits the inherent physicochemical properties of nanoparticles, such as size and surface charge, to take advantage of physiological phenomena like the EPR effect. The EPR effect can facilitate accumulation in tumors or inflamed tissues by allowing nanoparticles to permeate and be retained in areas with leaky vasculature. However, this effect varies greatly between tissue types and is often less robust in infectious or inflamed regions compared to solid tumors, resulting in inconsistent delivery outcomes.[155] Active targeting, in contrast, involves the functionalization of nanoparticle surfaces with specific ligands, such as antibodies, peptides, or small molecules, that bind to overexpressed or disease-specific receptors on target cells. While active targeting can enhance cellular uptake and specificity, it remains limited by numerous physiological barriers, including complex vascular architecture, extracellular matrices, variable blood flow, and immune clearance mechanisms. Additionally, variability in target receptor expression or downregulation in diseased tissues can further reduce targeting efficiency.[23,263]

Despite significant progress in nanoparticle engineering and targeting strategies, current evidence indicates that only a very small fraction often less than 1% of the systemically administered nanoparticle dose typically reaches the desired site of action.[21,22] The majority accumulates in off-target organs, which underscores the need for continued research to overcome biological and physiological barriers, enhance nanoparticle stability in circulation, and further optimize both passive and active targeting techniques. Achieving these advances is critical for the clinical translation and success of nanomedicine-based therapies, particularly for the treatment of infectious diseases and multidrug-resistant infections.

To overcome these challenges, several approaches are employed, including the use of FDA-approved polymers to manufacture nanoparticles, and collaboration with industry, educational institutions, and other regulatory departments to harmonize guidelines. Moreover, clinical trials are encouraged to utilize these nanoparticles in real-world settings, making the approval of safe nanomaterials possible.[264] The more clinical practice of this nanomaterial will also help to improve and specify the safety guidelines of these nanoparticles.

Recommendations

To understand the therapeutic potential of nanoparticles concerning antimicrobial resistance, different strategies have been used. Firstly, there is a need for nanoparticles to transition from in vitro studies to pre-clinical and clinical trials. For this purpose, translational studies are required for well-elaborated experimentation on animal models and then on early-phase human trials to evaluate the biosafety concerns, efficacy, and pharmacokinetics.[265] Secondly, more research is required on the dual-functional nanoparticles, the particles that deliver antibiotics, as well as factors that disrupt biofilms, influence immune response and specifically target the infection site. Introducing various stimuli, specific ligands, and other drugs can probably enhance the efficacy of these nanoparticles.[266] Thirdly, standardized protocols should be used to evaluate, characterize, and approve these nanoparticles; for this purpose, multidisciplinary collaborations of material scientists, microbiologists, pharmacists, and clinicians are encouraged. The combined efforts would contribute to the highly efficient innovation of these nanoparticles and also avoid redundant efforts. The open access to the data also promotes the rational design of more therapeutics and transparency.[267]

Moreover, different policy frameworks as well as funding agencies should play a role in scientific advancement, by providing funds, the commercialization of Nanomedicine could be made possible. By using these approaches, nanomedicine would play a role in treating several multidrug-resistant infections.[268]

Conclusion

Nanomedicine can greatly improve the fight against infections that resist multiple drugs by helping medicines better target problem areas, fighting biofilms, and preventing harsh side effects. Each nanomaterial adds a different way to solve microbial resistance. Nano-enabled testing helps identify infections early and correctly, which allows healthcare officers to begin the treatment sooner. Because antibiotics are used for both treatment and identification, we are seeing the emergence of theranostics in infectious diseases. Still, issues related to security, growth, and following rules remain a problem. To make progress, these problems must be investigated by thorough research, standardized approaches, and cooperation between different professions. Using the strengths of nanotechnology with artificial intelligence, precision medicine, and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology has the potential to greatly impact antimicrobial approaches in the future. More funding for studies, supportive government policies, and teamwork between public and private organizations will help nanomedicine treat antimicrobial resistance and guide efforts in controlling infectious diseases.

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