REVIEW ARTICLE

Nanotechnology-enabled Strategies to Overcome Antibiotic Resistance

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Abstract: Antimicrobial resistance is a growing global health challenge, with conventional antibiotics increasingly failing against multidrug-resistant and biofilm-associated infections. Nanotechnology offers promising solutions through enhanced antimicrobial activity, targeted drug delivery, and rapid diagnostics. This review discusses metallic, metal oxide, and hybrid nanoparticles that combat resistant pathogens via mechanisms including reactive oxygen species generation, membrane disruption, and quorum-sensing interference. Nanocarrier systems, such as liposomes, dendrimers, and polymeric nanoparticles, enhance drug delivery and restore antibiotic sensitivity. Nano-enabled diagnostic platforms, including biosensors and electrochemical systems, facilitate rapid detection of resistance markers at the point of care. Despite these advances, challenges related to toxicity, environmental impact, regulatory approval, and large-scale manufacturing remain. Emerging developments in green synthesis, artificial intelligence-guided design, and personalized nanomedicine may accelerate clinical translation. Overall, nanotechnology represents a versatile platform for improving the prevention, diagnosis, and treatment of antimicrobial-resistant infections.

KEYWORDS: Antimicrobial resistance, nanotechnology, nanomedicine, drug delivery, biosensors, biofilms, artificial intelligence

1. INTRODUCTION

Antimicrobial resistance (AMR) has emerged as one of the most critical public health challenges of the twenty-first century, threatening the effectiveness of modern medicine and undermining progress in infection control. According to a comprehensive global assessment, bacterial AMR was directly responsible for approximately 1.27 million deaths and associated with nearly 4.95 million deaths worldwide in 2019 (Murray et al., 2022). Recent assessments by the World Health Organization (WHO) have identified AMR as one of the top global public health threats, compromising the treatment of common infections and reducing the safety of routine medical procedures (WHO, 2023). Beyond its substantial mortality burden, AMR imposes profound socioeconomic consequences through prolonged hospitalization, escalating healthcare expenditures, reduced productivity, and diminished workforce participation. Economic projections suggest that, if left unchecked, AMR could reduce global gross domestic product by up to 3.8% annually by 2050 and force millions of individuals into extreme poverty (Jonas et al., 2017).

Furthermore, recent forecasting studies indicate that AMR-associated mortality is expected to increase substantially over the coming decades, particularly in low- and middle-income countries where healthcare systems face significant resource constraints (Lewnard et al., 2024). Infections that were once readily treatable, including pneumonia, urinary tract infections, bloodstream infections, and surgical-site infections, are

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increasingly difficult to manage due to the emergence and spread of multidrug-resistant (MDR) pathogens. These organisms evade antimicrobial therapy through a combination of enzymatic degradation, target modification, active efflux mechanisms, and biofilm-mediated protection, creating an urgent need for innovative therapeutic strategies.

The growing mismatch between the rapid evolution of AMR and the slow pace of antibiotic discovery has created a critical therapeutic gap. The World Health Organization has repeatedly highlighted the limited clinical antibacterial pipeline, noting that many newly developed agents represent modifications of existing antibiotic classes rather than truly novel therapeutic mechanisms. Concurrently, resistance rates among priority pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacterales*, and MDR *Pseudomonas aeruginosa*, continue to increase globally, reducing the effectiveness of conventional antimicrobial therapies (Marino et al., 2025). Collectively, these trends highlight the growing inadequacy of conventional antimicrobial development strategies and emphasize the need for alternative therapeutic platforms capable of overcoming established resistance mechanisms.

Although several antibacterial agents have been introduced in recent years, the pace of antibiotic innovation remains insufficient relative to the accelerating emergence and dissemination of resistant pathogens. The economic disincentive associated with antibiotic development further complicates this challenge, as limited financial returns discourage sustained investment in antimicrobial research and commercialization. Consequently, there is a pressing need for alternative therapeutic approaches that enhance the efficacy of existing antibiotics, restore susceptibility in resistant strains, and bypass conventional resistance mechanisms altogether.

Nanotechnology offers a novel frontier in this fight. Engineered nanomaterials exhibit unique physicochemical characteristics, including high surface-area-to-volume ratios, tunable surface functionalities, and enhanced interactions with microbial structures, enabling fundamentally different antimicrobial mechanisms compared to conventional antibiotics. Such mechanisms include membrane destabilization, intracellular reactive oxygen species (ROS) generation, disruption of metabolic pathways, and interference with nucleic acid integrity, thereby reducing susceptibility to many classical resistance mechanisms. Moreover, nanocarrier-based drug delivery systems can improve pharmacokinetic profiles, protect labile therapeutic agents from premature degradation, facilitate targeted drug delivery, and reduce systemic toxicity. Numerous studies have demonstrated that nanomaterial-based antimicrobial platforms enhance drug penetration, improve intracellular delivery, and potentiate antibacterial activity against MDR pathogens and biofilm-associated infections (Makabenta et al., 2021; Xie et al., 2025). In addition to therapeutic applications, nanotechnology has enabled the development of highly sensitive diagnostic platforms capable of rapid detection of AMR determinants, thereby supporting timely clinical decision-making and antimicrobial stewardship efforts.

Despite the promise, several challenges hinder widespread clinical adoption. These include potential nanotoxicity, off-target effects, and complex regulatory pathways. Recent advances in biodegradable, green-synthesized nanoparticles (NPs) and in silico modeling using artificial intelligence (AI) are expected to address these limitations (Tungare et al., 2024). Furthermore, ongoing progress in materials science, computational design, and translational nanomedicine is expected to improve the safety, efficacy, and scalability of next-generation nano-enabled antimicrobial interventions. This study aims to comprehensively review the role of nanotechnology-based approaches in combating antimicrobial resistance, focusing on their mechanisms of action, therapeutic potential, and challenges in clinical translation.

2. MECHANISMS OF ANTIBIOTIC RESISTANCE

Antibiotic resistance is a multifaceted adaptive phenomenon arising from genetic mutations, horizontal gene transfer, and physiological responses that collectively reduce bacterial susceptibility to antimicrobial agents. Resistance mechanisms can be systematically classified into five major categories: enzymatic degradation or modification of antibiotics, alteration of antimicrobial target sites, active efflux of antimicrobial compounds, reduced membrane permeability, and biofilm-mediated resistance (Figure 1). These mechanisms often act concurrently within the same pathogen, generating MDR phenotypes that complicate treatment strategies. The

following sections discuss each resistance pathway individually, highlighting their molecular basis and contribution to antimicrobial treatment failure.

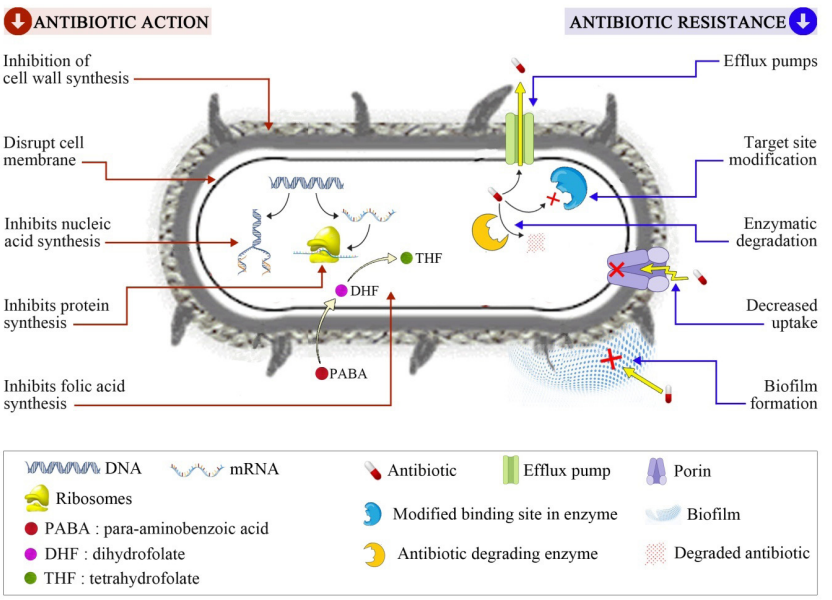


Figure 1. Schematic diagram illustrating key mechanisms of antibiotic action and bacterial resistance pathways

2.1. Enzymatic Inactivation and Efflux Systems

One of the earliest identified resistance strategies is enzymatic degradation. In a study by Gómez et al. (2023), bacteria expressing metallo-β-lactamases, such as NDM-1 and VIM, were shown to hydrolyze carbapenems with high efficiency, effectively neutralizing their antimicrobial activity. Similarly, Bharti and Kumar (2025) reported the extensive distribution of extended-spectrum β-lactamases (ESBLs) among *Escherichia coli* and *Klebsiella pneumoniae* strains, correlating this with increased treatment failure in urinary and bloodstream infections. Efflux pumps represent another formidable resistance strategy. These transmembrane protein complexes, such as the AcrAB-TolC system in Gram-negative bacteria, actively extrude antibiotics from the intracellular space, reducing drug accumulation below therapeutic thresholds. Overexpression of efflux pump genes under sub-MIC antibiotic exposure promotes persistent low-level resistance across multiple drug classes (Hetta et al., 2023).

2.2. Biofilm Formation and Structural Barriers

Biofilm-mediated resistance represents one of the most clinically challenging forms of antimicrobial tolerance and is implicated in a wide range of persistent infections, including those associated with indwelling medical devices, chronic wounds, and respiratory diseases (Ciofu et al., 2022). Biofilms consist of highly organized microbial communities embedded within a self-produced extracellular polymeric substance (EPS) matrix composed of polysaccharides, proteins, lipids, and extracellular DNA, which collectively create a protective microenvironment for bacterial survival. This matrix functions as both a physical and a chemical barrier, restricting antibiotic penetration, reducing immune cell accessibility, and facilitating microbial persistence (Ciofu et al., 2022). Furthermore, the heterogeneous architecture of biofilms generates gradients of oxygen, nutrients, and metabolic activity that promote the formation of dormant persister cells exhibiting markedly reduced susceptibility to antimicrobial agents (Rather et al., 2021). In addition to providing structural protection, biofilms facilitate horizontal gene transfer through enhanced

cell-to-cell interactions, thereby accelerating the dissemination of antibiotic resistance genes and contributing to the emergence and persistence of MDR bacterial populations (Almatroudi, 2025).

The resistance mechanisms described above present distinct therapeutic challenges that often limit the effectiveness of conventional antibiotics. Importantly, nanotechnology-based interventions have demonstrated the potential to overcome several of these barriers through diverse physicochemical and biological mechanisms. For example, nanoencapsulation can protect antibiotics from enzymatic degradation, while targeted nanocarriers enhance intracellular drug delivery and partially compensate for target-site modifications. Similarly, nanoparticle-mediated transport can enhance intracellular antibiotic accumulation and reduce the impact of efflux pumps. Metallic and carbon-based nanomaterials have also been reported to disrupt bacterial membranes, thereby enhancing permeability and facilitating antimicrobial uptake. Furthermore, the small size and tunable surface properties of NPs enable penetration into biofilm matrices, promoting biofilm disruption and improving the delivery of antimicrobial agents to otherwise protected bacterial populations. The following sections discuss the major classes of antimicrobial nanomaterials and their applications in overcoming these resistance mechanisms.

3. ANTIMICROBIAL NANOMATERIALS

Nanotechnology has opened a new frontier in antimicrobial therapy by introducing nanomaterials that operate via unconventional mechanisms, making them effective even against MDR and biofilm-forming bacteria. These agents exhibit strong activity through multi-modal action, as depicted in Figure 2, which highlights their mechanisms.

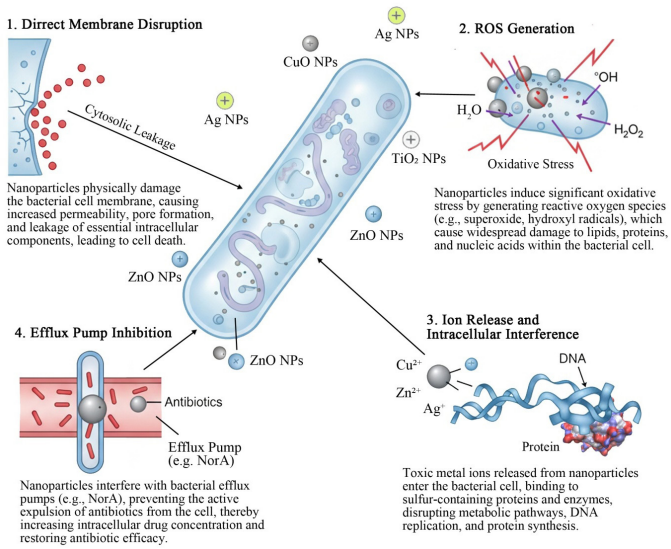


Figure 2. This schematic diagram illustrates the multi-modal antimicrobial mechanisms of metal nanoparticles in inactivating bacterial cells and bypassing bacterial resistance. The MNPs bypass inherent physical and chemical defences of bacteria, offering a significant advantage over single-target conventional antibiotics by employing a multi-target approach

3.1. Silver Nanoparticles (Ag NPs)

Ag NPs are among the most potent antimicrobial agents due to their multi-modal action involving membrane disruption, protein denaturation, and ROS generation. In a study by Abdulrahman and Nssaif (2016), Ag NPs combined with β-lactam antibiotics reduced the Minimum Inhibitory Concentration (MIC) against MRSA by up to 18 mm in zone diameter, indicating a strong synergistic effect. Similarly, in an *in vitro* comparison study, Ag NPs showed the lowest bacterial counts against Streptococcus mutans at equal concentrations compared with ZnO and TiO_2, highlighting their superior efficacy (Kambalyal et al., 2018).

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3.2. Zinc Oxide Nanoparticles (ZnO NPs)

ZnO NPs exhibit antimicrobial activity through mechanisms common to several metal-based nanomaterials, including ion-mediated cellular disruption and oxidative damage pathways (Table 1). A study by Van Hengel et al. (2020) demonstrated that ZnO NPs incorporated into titanium implants led to the complete eradication of MRSA in both *in vitro* and *ex vivo* murine femur models, especially when combined with silver, reducing required Ag levels by over 100-fold. ZnO was also shown to be more cytotoxic *in vitro* than Ag or TiO_2 in alveolar macrophages, emphasizing its potency and the need for dosage control (Liu et al., 2013).

Table 1. Comparative *in vitro* and *in vivo* antibacterial activity of metal-based nanoparticles

Nanoparticle	Mechanism	Target microorganisms	Quantitative efficacy	Synergy with antibiotics	Reference
Silver (Ag)	Membrane disruption, ROS	MRSA, *S. aureus, E. coli, C. albicans*	MIC ↓ up to 90%, zone ↑ 18 mm	Yes	(Abdulrahman & Nssaif, 2016)
Zinc oxide (ZnO)	ROS, membrane rupture	MRSA, *E. coli, P. aeruginosa*	Complete eradication in *ex vivo* bone model	Yes	(Van Hengel et al., 2020)
Titanium dioxide (TiO_2)	Photocatalytic ROS	*S. mutans, C. albicans*	7.5% loading inhibited growth significantly	Limited	(Giti et al., 2021)
Copper oxide (CuO)	Hydroxyl radical generation	*Salmonella, E. coli, S. aureus*	MIC < 10 μg/mL	Yes	(Duffy et al., 2018)
Selenium (Se)	Oxidative damage, DNA interference	*Staphylococcus, Bacillus*	MIC: 0.97–1.2 × 10^6 CFU/mL	Yes	(Staats et al., 2022)
Chitosan	Membrane adhesion, permeability loss	*A. hydrophila, E. coli, C. albicans*	Inhibition zone: 15–25 mm	Yes (with Ag, ZnO)	(Aly et al., 2023)
Cerium oxide (CeO_2)	Redox cycling, ROS buffering	*S. mutans, Enterococcus*	Enhanced antibiofilm action in dental models	Yes	(Yin et al., 2025)
Iron oxide (Fe_3O_4)	Membrane disruption, iron overload	*B. subtilis, P. aeruginosa*	MIC < 50 μg/mL	Yes	(Albalawi et al., 2020)
Graphene oxide	Physical slicing, oxidative stress	*S. aureus, E. coli*	99% bacterial reduction at 50 μg/mL	Limited	(Hasanin et al., 2023)
Copper-zinc-chitosan	Mixed ROS and chelation	*B. subtilis, A. brasiliensis*	MIC: 7.81–62.5 μg/mL	Yes	(Hasanin et al., 2023)

3.3. Titanium Dioxide Nanoparticles (TiO_2 NPs)

TiO_2 NPs are particularly interesting due to their photocatalytic properties. Under UV or visible light, TiO_2 exhibits photocatalytic antimicrobial activity through oxidative mechanisms. Studies have demonstrated the effective antibacterial, antifungal, and antiviral activities of TiO_2 with minimal toxicity, making it ideal for dental materials and medical coatings (Amiri et al., 2022). In another study, thermocycled polymethyl methacrylate (PMMA) reinforced with 7.5% TiO_2 significantly inhibited *Candida albicans* and *Streptococcus* species,

confirming its application in dentistry (Giti et al., 2021).

3.4. Copper Oxide Nanoparticles (CuO NPs)

CuO NPs act via Fenton-like reactions that produce hydroxyl radicals, contributing to membrane damage and protein oxidation. A study by Duffy et al. (2018) reported that CuO NPs showed strong *in vitro* activity against Salmonella and Campylobacter isolates from poultry, with MIC values comparable to or lower than those of Ag and ZnO NPs in certain strains (Duffy et al., 2018).

Despite their potent antimicrobial properties, concerns have emerged about the potential for microbial adaptation and resistance to metal-based NPs. Recent studies suggest that prolonged or sublethal exposure to NPs, particularly Ag NPs, may induce bacterial stress-response pathways, enhance efflux pump expression, promote biofilm formation, and select for genetic traits associated with metal tolerance. Furthermore, co-selection phenomena may occur when resistance determinants for metals and antibiotics are located on the same mobile genetic elements, potentially contributing to the dissemination of antimicrobial resistance. Although nanoparticle-mediated resistance appears less common than conventional antibiotic resistance, these findings highlight the importance of responsible nanoparticle design, dose optimization, and long-term environmental monitoring to minimize unintended development of resistance (Çelik et al., 2023). The major antimicrobial mechanisms of the nanomaterials described above are summarized in Table 2.

Table 2. Major antimicrobial mechanisms of nanomaterials against resistant bacteria

Mechanism	Representative nanomaterials	Antimicrobial effect
ROS generation	Ag NPs, ZnO NPs, CuO NPs, TiO_2 NPs	Oxidative damage to proteins, lipids and DNA
Membrane disruption	Ag NPs, graphene oxide, chitosan NPs	Increased permeability and cell lysis
Intracellular target interference	Ag NPs, Au NPs	DNA damage and enzyme inhibition
Quorum-sensing inhibition	Ag NPs, Se NPs	Reduced virulence and biofilm formation
Biofilm penetration and EPS disruption	Metallic NPs, dendrimers	Enhanced antibiotic penetration and biofilm eradication
Controlled antibiotic delivery	Liposomes, polymeric NPs	Improved drug accumulation and reduced resistance

4. NANOPARTICLE-MEDIATED DRUG DELIVERY SYSTEMS

One of the most transformative applications of nanotechnology in infectious disease management is in antibiotic delivery. Traditional antibiotics often face significant limitations, such as low bioavailability, poor tissue penetration, rapid systemic clearance, and nonspecific toxicity. Nanoparticle-based drug delivery systems overcome many barriers by enhancing solubility, prolonging circulation time, enabling targeted delivery, and protecting antibiotics from enzymatic degradation (Nagarajan et al., 2024; Usharani et al., 2023). The specific properties, benefits, and drawbacks of different nanoparticle carriers are outlined in Figure 3.

4.1. Liposomes: Versatile Antibiotic Carriers

Liposomes are spherical vesicles composed of phospholipid bilayers encapsulating hydrophilic or hydrophobic drugs. Their size, charge, and composition can be tuned for optimal delivery. Liposomal formulations of vancomycin and ciprofloxacin demonstrated up to a five-fold increase in accumulation at infection sites compared to free drug, while also reducing nephrotoxicity and hepatotoxicity in preclinical models (Ferreira et al., 2021). Another study by Imran et al. (2022) reported

that cationic liposomes adhered preferentially to bacterial cell walls and biofilms, thereby enhancing delivery and antimicrobial activity, even against MDR *P. aeruginosa* strains. Nanoparticle-fraught liposomes containing PLGA cores demonstrated an 8-fold increase in antibiotic selectivity toward *P. aeruginosa*, and significantly reduced toxicity to mammalian cells in respiratory infections (Fakhoury et al., 2024). In ocular keratitis models, the same liposomal systems delivered complete bacterial clearance with lower levels of TNF-α and IL-6, indicating improved anti-inflammatory profiles (Fakhoury et al., 2024).

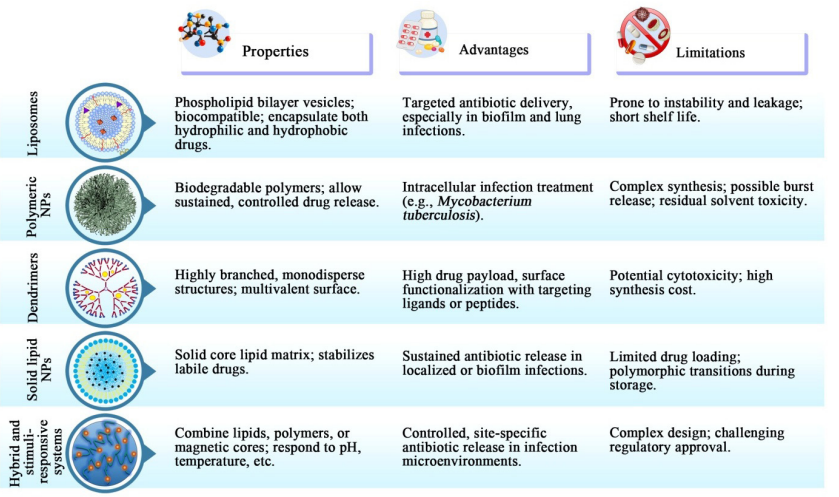


Figure 3. Schematic representation of nanoparticle-based drug delivery systems, showcasing their uses and limitations in antibiotic delivery and therapeutic precision

4.2. Polymeric NPs: Controlled Release Vehicles

Polymeric NPs offer tunable release kinetics and improved drug encapsulation efficiency. In a recent study, poly(lactic-co-glycolic acid) (PLGA) NPs loaded with linezolid exhibited sustained drug release over 72 hours and achieved complete eradication of intracellular *Mycobacterium tuberculosis* in infected macrophages *in vitro* (Moradialvand et al., 2024; Pal et al., 2025). Polymeric micelles also play a pivotal role in solubilizing poorly water-soluble antibiotics, such as rifampicin and amphotericin B, while enabling pH-sensitive release at acidic infection sites (Zong et al., 2022).

4.3. Dendrimers: Multibranched Targeted Carriers

Dendrimers are monodisperse, tree-like structures that offer multivalent surfaces for loading and targeting moieties. In tuberculosis treatment, poly(amidoamine) dendrimers loaded with isoniazid enhanced intracellular drug delivery via aerosol administration, reduced dose requirements, and maintained therapeutic efficacy (Shukla et al., 2020). In another study, vancomycin-loaded lipid–dendrimer hybrids showed 8-fold lower MICs against MRSA and 84% bacterial killing, while maintaining low toxicity in mammalian cells (Maji et al., 2019). In another study, Alfei and Schito (2020) reported that poly(amidoamine) (PAMAM) dendrimers functionalized with antimicrobial peptides not only enhanced drug payload but also demonstrated innate antibacterial activity against resistant Gram-negative strains. These systems showed MIC reductions of over 90 percent for ciprofloxacin when administered as dendrimer conjugates.

4.4. Solid Lipid Nanoparticles (SLNS): Stability and Biofilm Penetration

SLNs are composed of biocompatible lipids and offer superior stability, especially for labile drugs. In pulmonary TB, mannosylated SLNs demonstrated enhanced uptake by alveolar macrophages and reduced bacterial burden with lower systemic exposure (Carneiro & dos Santos, 2020). In biofilm-associated catheter infections, ceftriaxone-loaded SLNs maintained bactericidal activity for 48 hours post-application, preventing recurrence (Vassallo

et al., 2020; Zong et al., 2022). These formulations reduce burst release and maintain therapeutic levels within localized infection niches.

4.5. Hybrid Nanocarriers and stimuli-responsive Systems

Hybrid carriers, such as lipid–polymer NPs or dendrimer–lipid composites, combine the advantages of both systems and can be engineered for external triggers (pH, temperature, magnetic fields). The synergy between nanocarrier structural design and antibiotic pharmacodynamics has been identified as a key determinant in overcoming bacterial tolerance and intracellular persistence (Vassallo et al., 2020). By modulating spatial and temporal drug delivery, these nanoparticle systems provide a rational framework for maximizing therapeutic efficacy, minimizing the emergence of resistance, and reducing systemic toxicity. In a study on pH-responsive lipid–dendrimer hybrids, vancomycin was released 1.5 times faster at acidic pH than at neutral pH, reflecting the microenvironment of infection sites. These formulations resulted in sustained MRSA killing over 72 hours (Sonawane et al., 2016).

A comparative overview of the major nanomaterial platforms for combating AMR is presented in Table 3, highlighting their key advantages, limitations, clinical readiness levels, and representative applications. This comparison facilitates the identification of current translational barriers and future research priorities for the successful clinical implementation of nanotechnology-based antimicrobial strategies. Although numerous nanomaterial platforms have demonstrated promising antimicrobial activity, their translational potential varies considerably. Metallic NPs often exhibit strong intrinsic antibacterial effects but may raise concerns regarding toxicity and environmental persistence. In contrast, lipid- and polymer-based nanocarriers generally offer superior biocompatibility and drug-delivery performance but frequently lack intrinsic antimicrobial activity. Furthermore, despite encouraging preclinical results, only a limited number of nano-enabled antimicrobial systems have progressed toward clinical evaluation, highlighting the need for standardized safety assessment, scalable manufacturing strategies, and regulatory frameworks to facilitate clinical translation.

Table 3. Critical comparison of nanomaterial platforms for combating antimicrobial resistance

Nanomaterials	Major advantages	Key limitations	Clinical readiness	Applications
Ag NPs	Broad-spectrum antibacterial activity, ROS generation and biofilm disruption	Cytotoxicity concerns, environmental accumulation and potential adaptive bacterial responses	Advanced preclinical	Wound dressings and implant coatings
Au NPs	Excellent biocompatibility, facile surface functionalization and diagnostic applications	Limited intrinsic antibacterial activity and high production cost	Preclinical	Drug delivery, biosensing and photothermal therapy
ZnO NPs	Strong ROS-mediated antimicrobial effects and low-cost synthesis	Dose-dependent toxicity and stability concerns	Preclinical	Biofilm inhibition and antimicrobial coatings
TiO_2 NPs	Photocatalytic antibacterial activity and surface coating applications	UV-light dependence and oxidative toxicity concerns	Preclinical	Medical-device coatings and disinfection
Polymeric NPs	Controlled drug release, enhanced pharmacokinetics and protection from degradation	Manufacturing complexity and scalability challenges	Advanced preclinical	Antibiotic delivery systems

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Table 3. Continued

Nanomaterials	Major advantages	Key limitations	Clinical readiness	Applications
Liposomes	High biocompatibility and functions as a clinically established delivery platform	Stability limitations and higher production costs	Early clinical/ preclinical	Encapsulation of antibiotics and targeted delivery
Dendrimers	High drug-loading capacity and tunable surface chemistry	Potential cytotoxicity and expensive synthesis	Preclinical	Biofilm-targeted antimicrobial therapy

5. NANOTECHNOLOGY IN BIOFILM DISRUPTION

Biofilms significantly contribute to chronic infections and AMR by protecting bacteria within an extracellular matrix of polysaccharides, proteins, and DNA. Nanotechnology provides innovative solutions to prevent biofilm formation, disrupt mature structures, enhance antibiotic penetration through EPS matrices, and enable targeted antimicrobial delivery (Ciofu et al., 2022). Recent studies have demonstrated that NPs can physically degrade biofilm matrices, interfere with quorum-sensing (QS) pathways, inhibit bacterial adhesion and microcolony formation, and significantly improve antimicrobial efficacy against biofilm-associated infections (Koo et al., 2017). Figure 4 conceptually outlines these advanced nanotechnology-mediated strategies to overcome biofilm resistance.

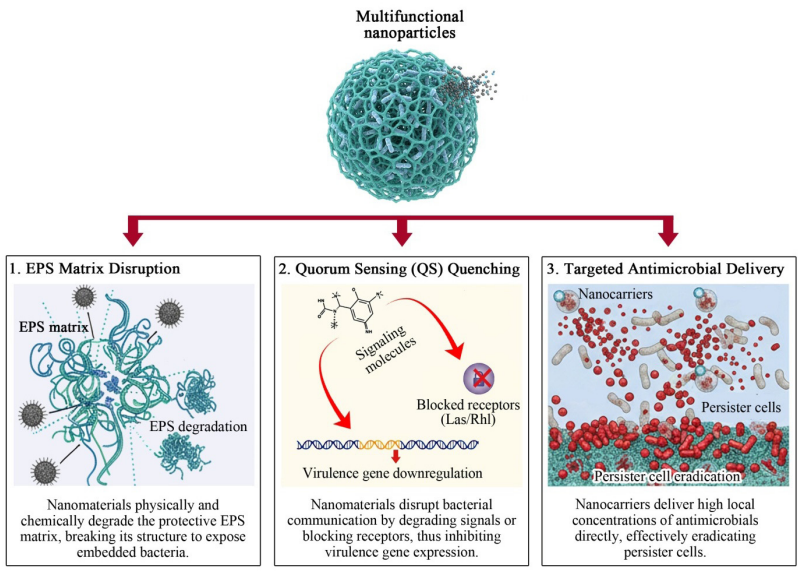


Figure 4. A schematic representation of a nanotechnology-driven approach for biofilm eradication: (1) disruption of the EPS matrix, (2) quenching of bacterial Quorum Sensing, and (3) targeted delivery of antimicrobials to overcome resistance

5.1. Nanoparticle-mediated Matrix Disruption

Metallic NPs, especially Ag NPs, have demonstrated potent antibiofilm activity. Proteomics-guided analysis demonstrated that Ag NPs effectively disrupted mature *P. aeruginosa* biofilms, leading to reduced biomass and extracellular matrix degradation. This effect was associated with disruption of multiple cellular pathways involved in biofilm maintenance, including iron metabolism and adhesion-related processes (Zhang et al., 2020). Scanning electron microscopy confirmed substantial disruption of mature biofilm architecture within 24 h, accompanied by enhanced antimicrobial penetration

into deeper biofilm layers and increased bacterial susceptibility.

ZnO NPs synthesized using plant extracts also reduced biofilm integrity by over 60% in *P. aeruginosa*, mainly through exopolysaccharide degradation and reduction of swarming motility. MIC was determined to be 1600 µg/mL, and EPS disruption was confirmed by *in vitro* assays and QS docking studies with Las and Rhl regulators (Ali et al., 2021). Recent studies have further demonstrated that nanozymes and catalytic nanomaterials can degrade key EPS components, including extracellular DNA and polysaccharides, thereby weakening biofilm cohesion and facilitating antibiotic diffusion throughout mature biofilm structures (Chen et al., 2024).

5.2. Quorum-sensing Interference and Signal Disruption

Interference with bacterial communication pathways is another powerful strategy. Biogenic NPs synthesized from microbial proteins disrupted signal cascades by reducing acyl-homoserine lactone (AHL) production, down-regulating biofilm-forming genes, and silencing quorum-sensing genes such as LasI and RhlI (Lahiri et al., 2021). Similarly, selenium NPs inhibited violacein production in *Chromobacterium violaceum* and reduced *P. aeruginosa* biovolume by 80%, showing broad-spectrum quorum quenching effects (Gómez-Gómez et al., 2019). In another study, Ag NPs capped with aminocellulose and quorum-quenching enzymes completely inhibited biofilm formation and suppressed 45% of QS-regulated virulence genes at an 8-fold lower concentration than unmodified Ag NPs (Ivanova et al., 2020).

Beyond disrupting established biofilms, quorum-sensing inhibition represents an effective strategy for preventing initial biofilm formation. By suppressing bacterial communication pathways involved in adhesion, microcolony development, and virulence expression, nanomaterials can inhibit biofilm formation before mature structures form (Xue et al., 2024).

5.3. Multifunctional and Responsive Nanoplatforms

Stimuli-responsive and multifunctional systems offer superior control over biofilm eradication. Luo et al. (2024) developed hyaluronic-acid-coated ferrite NPs that disrupted QS-related genes (agrA, agrC) and enhanced thermal ablation of biofilms via magnetic hyperthermia. *In vivo*, this system led to full biofilm clearance and reduced inflammation in murine models. Another promising platform combined tobramycin with a lipophilic quorum-sensing inhibitor in squalenyl hydrogen sulfate NPs. This formulation eradicated *P. aeruginosa* biofilms at tobramycin concentrations 16-fold lower than those of free drug, demonstrating synergistic action in mucin and tracheal mucus environments (Ho et al., 2020).

Stimuli-responsive nanoplatforms also enhance antibiotic penetration within dense biofilm matrices by releasing antimicrobial agents in response to local physicochemical triggers, such as pH gradients, enzymatic activity, and redox conditions characteristic of mature biofilms. Such targeted release improves local drug concentrations, enhances biofilm eradication, and minimizes systemic exposure and off-target toxicity (Koo et al., 2017).

5.4. *In vivo* Relevance and Clinical Potential

Beyond lab assays, *in vivo* studies validate nanoparticle systems for biofilm disruption in catheter, wound, and lung infection models. For example, dendrimer-based vancomycin delivery systems demonstrated 84% bacterial killing and reduced recurrence in catheter-associated infections (Maji et al., 2019). Bharti and Kumar (2025) documented enhanced therapeutic outcomes in murine models of catheter-associated infections when using antibiotic-loaded NPs. These systems showed significant reductions in biofilm biomass and recurrence rates compared to free antibiotics. Studies have demonstrated that nanocarrier systems effectively reduced fungal biofilms of *Candida albicans*, which often co-exist with bacteria in polymicrobial infections (Cai & Kim, 2023; Ma et al., 2020). In dental biofilms, which are notoriously persistent, NPs have demonstrated marked success. The incorporation of TiO_2 and Ag-based NPs into dental coatings can significantly reduce biofilm formation on implants and orthodontic appliances. These particles penetrated biofilm layers and exerted potent antimicrobial effects, thereby contributing to reduced biofilm formation and persistence (Hetta et al., 2023).

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Collectively, these studies highlight the considerable potential of NPs as tools for biofilm control through physical, chemical, and biological interactions. However, most evidence remains derived from *in vitro* and preclinical investigations, and further studies are needed to establish long-term safety, efficacy, and clinical applicability.

6. NANOTECHNOLOGY-ENABLED DIAGNOSTICS FOR AMR

The rapid and accurate diagnosis of AMR is essential for initiating timely treatment, preventing inappropriate antibiotic use, and reducing the evolution of resistance. Traditional diagnostic tools, though reliable, are time-consuming and infrastructure-dependent. In contrast, nanotechnology-based diagnostics offer fast, portable, and highly sensitive platforms that leverage unique nanoscale properties, such as surface plasmon resonance (SPR), high surface-area-to-volume ratios, and engineered surface chemistries. Some recent nano-enabled diagnostic platforms, along with their detection modes, microbial targets, sensitivities, and time-to-result, are summarized in Table 4. These innovations have led to the development of biosensors and point-of-care systems capable of detecting resistance genes, enzymatic activity, and viable bacteria within minutes to a few hours.

Table 4. Some recent nano-enabled diagnostic platforms for rapid and sensitive detection of AMR

Nanotechnology platform	Detection Type	Target	Time	Sensitivity	Reference
RAPIDx SPR chip	Optical (SPR + enzyme)	β-lactamase, resistance genes	45 min	Near 100%	(Lee et al., 2025)
Quantum dot ZnO SPR sensor	Optical (SPR/ fluorescence)	miRNA-21 (resistance marker)	<1 h	Attomolar	(Wang et al., 2023)
LSPR quantum Dot sensor	Optical (LSPR)	H1N1, H3N2 virus	–	0.03 pg/mL (H1N1), 10 PFU/mL (H3N2)	(Takemura et al., 2017)
Chitosan gold strip	Colorimetric	β-lactamase	30 min	100% specificity	(Punjabi et al., 2020)
Copper-mediated plasmonic sensor	Visual aggregation	MDR bacteria (copper metabolism)	3 h	95.8%	(Zhang et al., 2024)
Dextrin AuNP biosensor	Colorimetric	blaKPC-positive *K. pneumoniae*	30 min	~10^3 CFU/mL, 97% specificity	(Caliskan-Aydogan et al., 2023)
Oligo-gold multiplex sensor	Colorimetric	*Salmonella* (19 strains)	<30 min	<10 CFU/mL	(Quintela et al., 2019)
Gold NP electrochemical sensor	Electrochemical + AI	AMR genes	<1 h	High specificity	(Taha et al., 2024)
Graphene-QD biosensor	Electrochemical	Rifampin-resistant TB	<1 h	10 CFU/mL	(Rabti et al., 2020)
SERS Au@Ag nanorods	Raman spectroscopy	*E. coli* resistance profile	3.5 h	10^2 CFU/mL	(Bi et al., 2020)
SERS dual-mode PB MOF sensor	Raman + colorimetric	*S. aureus*, *E. coli*	<1 h	6 CFU/mL	(Cai et al., 2023).
Smartphone AI theranostic	Optical + AI	AMR pathogens	<1 h	Field deployment ready	(Saxena et al., 2022).

6.1. Optical and Plasmonic Nanosensors

Optical nanosensors based on surface SPR, whispering-gallery-mode resonators, and fluorescence platforms have demonstrated high specificity and speed in AMR detection. A device called RAPIDx was developed to detect resistance genes and β-lactamase activity within 45 minutes using photothermal lysis and rolling circle amplification, achieving near-complete phenotype-genotype agreement (Lee et al., 2025). Similarly, an SPR-enhanced biosensor utilizing copper-indium quantum dots and doped ZnO nanorods achieved attomolar sensitivity for miRNA markers linked to resistance, demonstrating utility in lab-on-paper diagnostics (Wang et al., 2023). In another study, a localized surface plasmon resonance (LSPR) quantum dot-based system was developed for viral detection, achieving a detection limit of 0.03 pg/mL for H1N1 and 10 PFU/mL for H3N2 using dual-target immunofluorescence capture, suggesting strong potential for multiplex AMR biosensing applications (Takemura et al., 2017). Further expanding the scope, optical biosensors for antibiotic surveillance were described for monitoring misuse and overuse, particularly in livestock and clinical settings, using SPR and fluorescence platforms (Chaudhary et al., 2024).

6.2. Colorimetric and Quantum Dot-based Biosensors

Colorimetric biosensors based on nanoparticle aggregation provide a simple, rapid means of detecting antimicrobial resistance. A sensor exploiting bacterial copper metabolism could distinguish resistant from sensitive strains by triggering gold nanoparticle aggregation, achieving 95.8 percent sensitivity within 3 hours (Zhang et al., 2024). Another paper-based biosensor using chitosan-coated NPs demonstrated 100 percent specificity in identifying β-lactam resistance in validated clinical samples within 30 minutes (Punjabi et al., 2020). A rapid colorimetric assay developed using dextrin-coated Au NPs successfully detected carbapenem-resistant *Klebsiella pneumoniae* harboring the blaKPC gene in just 30 minutes, with 97 percent specificity and a detection limit of approximately 10^3 CFU/mL (Caliskan-Aydogan et al., 2023). In another study, a multiplex colorimetric platform using oligonucleotide-functionalized Au NPs simultaneously detected 19 Salmonella serotypes in food samples, achieving a sensitivity of <10 CFU/mL (Quintela et al., 2019).

6.3. Electrochemical and Magnetic Biosensors

Electrochemical biosensors exploit electron transfer at nanostructured electrodes to detect specific bacterial DNA or resistance proteins. Taha et al. (2024) demonstrated an AI-integrated electrochemical biosensor using Au NPs for under-one-hour profiling of AMR genes. In another study, graphene-quantum dot hybrids were also shown to detect rifampin-resistant tuberculosis at concentrations as low as 10 CFU/mL (Rabti et al., 2020). A recent study by Hsu et al. (2024) reviewed electrochemical-optical dual-mode sensors capable of combining fluorescence or SERS with voltammetry to improve accuracy and range for foodborne pathogen diagnostics

6.4. Surface-enhanced Raman Scattering (SERS) and Smart Sensing

SERS-based diagnostics can amplify molecular vibrational signals to detect bacterial resistance markers. One system using Au@Ag nanorods identified *E. coli* and resistance phenotypes within 3.5 hours, with a detection limit of 10^2 CFU/mL (Bi et al., 2020). A recent dual-mode biosensor achieved a detection limit of 6 CFU/mL and enabled SERS/colorimetric discrimination of *S. aureus* and *E. coli* with peroxidase-like nanozyme amplification (Cai et al., 2023). A smartphone-compatible version developed by Zhao et al. (2025) achieved detection down to 1 CFU/mL in milk samples with 98.6% capture efficiency using lectin-functionalized magnetic particles.

6.5. Artificial Intelligence Integration and Field Diagnostics

Several innovative diagnostic platforms now combine nanobiosensors with artificial intelligence and cloud-based IoT interfaces to support rapid decision-making and field deployment. A smart theranostic platform using upconversion NPs and mobile phones was shown to identify AMR pathogens and deliver targeted antimicrobials simultaneously, with measurable reductions in readmission rates in pilot trials (Saxena et al., 2022). In another study, Cui et al. (2024) developed an AI-assisted colorimetric system using YOLOv5 to detect bacterial enzyme

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activity, achieving a detection limit of 10 CFU/mL and 100% sensitivity in clinical validation.

7. SAFETY, BIOCOMPATIBILITY AND TOXICITY OF ANTIMICROBIAL NANOMATERIALS

NPs offer significant promise in combating antimicrobial resistance, but concerns over cytotoxicity, genotoxicity, and immunotoxicity limit their clinical translation. These adverse effects often depend on dose, size and surface chemistry and may vary across biological systems and microbial targets. Therefore, understanding their interaction with host cells, microbial flora, and tissues is critical for safe implementation. Ag NPs, ZnO NPs and TiO_2 NPs are among the most studied antimicrobial NPs. Ag NPs were found to induce significant DNA strand breaks in TK6 lymphoblast cells *in vitro*, as confirmed by comet assays, although no mutation frequency increase was detected in the PIG-A gene (Zhu et al., 2020). In an *in vivo* rat study, Ag NPs administered intravenously (5–10 mg/kg) induced sustained micronucleus formation in bone marrow erythrocytes, even 4 weeks after exposure (Dobrzyńska et al., 2014). A study conducted by McCracken (2015) reported that Ag NPs enhanced bacterial clearance in *S. aureus* infections but also impaired mitochondrial function in Caco-2 cells at <10 µg/mL. ZnO NPs exhibit significant cytotoxicity due to the release of Zn^{2+} ions, which disrupt mitochondrial function and induce ROS-mediated damage (Segura et al., 2024). Studies have reported that ZnO NPs exhibit 65.2% hemolysis in human red blood cells at 250 ppm, along with oxidative stress responses like depleted glutathione and increased lipid peroxidation (Khan et al., 2015).

In contrast, TiO_2 NPs are generally considered less toxic but can cause DNA damage at high doses or prolonged exposure. TiO_2 NPs have been associated with DNA damage in lung epithelial (A549) and lymphoblast (TK6) cells, even at non-cytotoxic concentrations, due to oxidative stress (El Yamani et al., 2017). In rat models, chronic exposure to food-grade TiO_2 (E171) led to mitochondrial damage in cardiomyocytes, including altered binding of adenine nucleotide translocase and increased systolic blood pressure (Correa Segura et al., 2024). Interestingly, when ZnO and TiO_2 were combined in murine models, the composite NPs showed synergistic toxicity, evidenced by oxidative stress in hepatic and renal tissues and increased micronuclei formation in bone marrow cells (Fadoju et al., 2019). However, in some models, co-administered TiO_2 attenuated ZnO's DNA damage, potentially by adsorbing zinc ions and enhancing DNA repair (Hackenberg et al., 2017).

Therefore, the antimicrobial efficacy of these NPs must be carefully balanced against their potential toxicological effects. Several strategies have been developed to mitigate nanoparticle-associated toxicity, including surface functionalization, biocompatible coatings, controlled-release formulations, and green synthesis approaches. Surface modification using polymers such as polyethylene glycol (PEG) and chitosan can improve colloidal stability, reduce nonspecific cellular interactions, and enhance biocompatibility while maintaining antimicrobial performance (Osman et al., 2022). Similarly, biomimetic and biodegradable nanocarriers have demonstrated reduced systemic toxicity and improved biological compatibility compared with conventional nanomaterials (Kang et al., 2024). Green synthesis strategies employing plant extracts, microbial products, and other biological resources have also emerged as promising alternatives to minimize hazardous reagents and improve environmental safety. Furthermore, establishing standardized safety evaluation frameworks, including hemocompatibility testing, genotoxicity assessment, biodistribution studies, and long-term toxicity monitoring, remains essential for defining clinically acceptable exposure limits and facilitating regulatory approval of antimicrobial nanomaterials (Parvin et al., 2025; Rabiee, 2025). A comprehensive overview of the *in vitro* and *in vivo* toxicity profiles, dose-dependent adverse effects, and safety observations reported for commonly used antimicrobial NPs is presented in Table 5.

8. CHALLENGES AND FUTURE PERSPECTIVES

Despite remarkable advances in nanotechnology for AMR management, the road to clinical and societal implementation is fraught with several challenges. These barriers range from technical and translational bottlenecks to regulatory ambiguity and environmental sustainability. As illustrated in Figure 5, successful translation of nano-antimicrobials requires coordinated progress across development, manufacturing, regulatory, and post-market stages.

Table 5. *In vitro* and *in vivo* toxicity profiles of common antimicrobial nanomaterials

Nanoparticle	Biological effect	Model system	Dose/concentration	Key findings	Reference
Ag NPs	Genotoxicity, DNA strand breaks	TK6 lymphoblasts	200 μmol/L	DNA damage without PIG-A mutation	(Zhu et al., 2020)
Ag NPs	Micronucleus formation	Rat bone marrow	5–10 mg/kg (i.v.)	Sustained DNA damage up to 4 weeks	(Dobrzyńska et al., 2014)
Ag NPs	Mitochondrial dysfunction	Caco-2 cells	<10 μg/mL	76% reduction in mitochondrial activity	(McCracken, 2015)
ZnO NPs	Hemolysis, oxidative stress	Human erythrocytes	250 ppm	65% hemolysis, ROS generation	(Khan et al., 2015)
ZnO NPs	Autophagy, genotoxicity	Human keratinocytes	<10 μg/mL	Induced autophagy and inflammasome activation	(Zhao, 2015)
TiO_2 NPs	Oxidative DNA damage	A549, TK6 cells	≤50 μg/mL	DNA strand breaks at sublethal levels	(El Yamani et al., 2017)
TiO_2 (E171) + ZnO	Cardiotoxicity, mitochondrial stress	Rats	Oral, 45 days	mPTP disruption, 50% drop in aconitase activity	(Correa Segura et al., 2024)
TiO_2 + ZnO NPs	Micronucleus induction, hepatotoxicity	Swiss mice	9.38–150 mg/kg	Synergistic toxicity in the liver and bone marrow	(Fadoju et al., 2019)
TiO_2 antagonizing ZnO	DNA repair enhancement	Nasal mucosa culture	0.1–20 μg/mL	TiO_2 reduced ZnO-induced genotoxicity	(Hackenberg et al., 2017)

Addressing these hurdles systematically is critical for realizing the full potential of nano-antimicrobials in real-world healthcare.

8.1. Clinical Translation Barriers

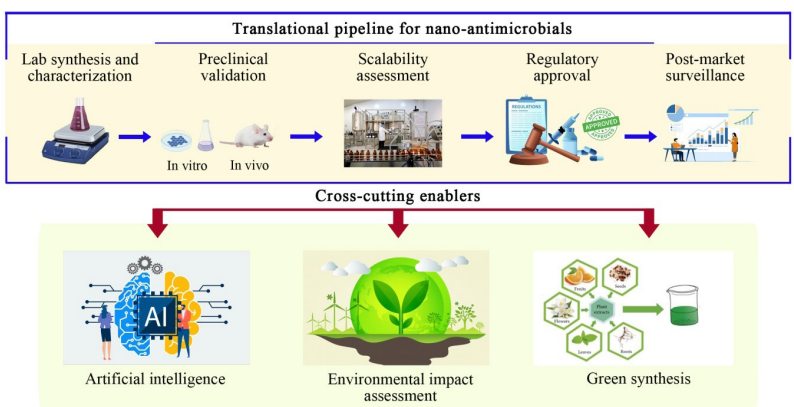


Figure 5. Translational roadmap for nano-antimicrobials, illustrating the key stages from laboratory development to clinical implementation and the cross-cutting enablers that support successful translation

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Table 5. Continued

Nanoparticle	Biological effect	Model system	Dose/concentration	Key findings	Reference
TiO_2 NPs	Minimal cytotoxicity	HepG2 cells	>75 $\mu g/cm^2$	No DNA strand breaks or viability loss	(Elje et al., 2020)
ZnO + TiO_2 NPs	Systemic organ damage	Swiss mice	9.38–150 mg/kg	Hepatic and renal damage, synergistic toxicity	(Ogunsuyi et al., 2022)

NPs with proven *in vitro* antimicrobial activity often fail to yield consistent results in animal models or humans due to challenges with pharmacokinetics, immune clearance, and tissue distribution. Se NPs, while potent against S. aureus and P. aeruginosa, face limitations due to variable biodistribution and uncertain long-term tissue retention (Truong et al., 2021). A major bottleneck in clinical translation is the lack of standardized toxicity protocols, leading to inconsistent safety profiles across studies (Ioannou et al., 2024).

Despite these challenges, several nanomedicine platforms have successfully reached clinical practice, demonstrating the translational feasibility of nanoparticle-based therapeutics. Liposomal formulations such as AmBisome® (liposomal amphotericin B), Doxil® (pegylated liposomal doxorubicin), and Onivyde® (liposomal irinotecan) have received regulatory approval and established the clinical utility of nanocarrier systems by improving drug pharmacokinetics and reducing systemic toxicity (Barenholz, 2012; Bulbake et al., 2017). Although these approved nanomedicines were developed primarily for oncology and fungal infections, their successful translation highlights the potential of nanotechnology-based platforms to overcome key barriers associated with drug delivery, safety, and therapeutic efficacy. Nevertheless, the clinical application of nano-enabled antimicrobial therapies remains at an early stage, underscoring the need for robust clinical validation, standardized regulatory pathways, and long-term safety assessments before widespread adoption can be achieved.

8.2. Scalable Manufacturing and Cost

While many nanoformulations demonstrate efficacy at the lab scale, their large-scale synthesis is rarely feasible with the same precision and purity. Parameters like particle size, zeta potential, and encapsulation efficiency may vary during industrial production. Biogenic nanomaterials, such as those derived from plant extracts or agro-waste, offer lower costs and eco-friendliness but suffer from batch-to-batch variability (Barsola et al., 2024). Efforts to implement GMP-compliant, reproducible protocols for nanoparticle synthesis remain scarce and underfunded (Bharti & Kumar, 2025). Scalability assessment represents a critical step in the translational pipeline, linking laboratory-scale innovation to industrial production.

8.3. Regulatory and Ethical Issues

The regulatory landscape for nanomedicine is complex and fragmented. Agencies like the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have not issued unified guidelines for nano-antimicrobials. A lack of dedicated nanoparticle approval pathways delays clinical testing and market entry. Furthermore, ethical concerns arise regarding the use of nanoparticles in vulnerable populations and ecosystems, especially when their long-term effects are unknown (Mishra et al., 2025). Interdisciplinary collaborations are urgently needed to develop risk-benefit assessment tools tailored to the nanoscale.

8.4. Integration with AI and Precision Medicine

AI can revolutionize nanoformulation by predicting optimal nanoparticle size, drug loading efficiency, and target selectivity. AI-guided machine learning models are already being trained on antimicrobial susceptibility databases to design optimized nanoparticle combinations (Fagbemi et al., 2025). However, these tools require large, curated datasets, which are often not publicly available. Furthermore, regulatory bodies must develop frameworks for AI-informed diagnostics and treatments, especially

in personalized or decentralized healthcare environments (Saxena et al., 2022).

8.5. Sustainable and Green Nanotechnology

Environmental impact assessment and green synthesis are increasingly recognized as essential components of responsible nano-antimicrobial development. Conventional synthesis of NPs often involves toxic solvents and energy-intensive protocols. Recent approaches use waste-derived materials, such as coffee husks and plant extracts, for the synthesis of ZnO nanoparticles, achieving bactericidal activity against *Salmonella* species and *S. aureus* with high biocompatibility (Sandeep et al., 2024). Yet, the long-term environmental impact of widespread nano-release is underexplored. Sustainable nanotechnology must integrate life-cycle assessment, circular economy frameworks, and environmental impact modelling (Pokrajac et al., 2021).

Despite substantial progress in nanotechnology-based antimicrobial research, much of the current evidence is derived from individual laboratory-scale studies conducted under controlled experimental conditions. Variations in nanoparticle synthesis methods, bacterial strains, testing protocols, and outcome measures often limit direct comparisons across studies. Consequently, caution should be exercised when interpreting reported antimicrobial efficacy, and broader validation through standardized methodologies, large-animal models, and clinical investigations is required before widespread clinical adoption can be achieved. Nevertheless, the successful regulatory approval of several nanomedicine products in other therapeutic areas demonstrates that the translational pathway for nano-enabled antimicrobial therapies is achievable when supported by robust safety, manufacturing, and clinical evidence.

9. CONCLUSION

Nanotechnology has emerged as a promising frontier in addressing the global challenge of antimicrobial resistance. From advanced drug delivery systems such as liposomes, dendrimers, and solid lipid NPs to ultra-sensitive diagnostic tools like plasmonic biosensors, SERS platforms, and electrochemical sensors, nano-enabled approaches have significantly enhanced the precision, speed, and effectiveness of AMR detection and treatment. Despite these advances, key challenges persist. Translational barriers such as toxicity concerns, variability in biological responses, lack of scalable synthesis protocols, and regulatory uncertainties continue to limit clinical adoption. Additionally, the environmental footprint and long-term biosafety of these materials remain underexplored. Encouragingly, recent developments in green nanotechnology, AI-driven design, and integrated diagnostics are beginning to bridge these gaps. Moving forward, the safe, scalable, and ethically sound integration of nanotechnology into AMR strategies will require interdisciplinary collaboration, standardized evaluation frameworks, and proactive regulatory support. If these elements align, nano-antimicrobials can redefine infection control in clinical and public health settings, providing faster, more targeted, and more sustainable solutions for a post-antibiotic world.

Highlights

- Nanomaterials show strong activity against resistant and biofilm-forming microbes.

- Nanocarriers improve drug delivery, reduce toxicity, and enhance targeting.

- Nano-based sensors enable rapid and sensitive AMR detection.

- AI and green synthesis support safe and scalable nanotechnology solutions.

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Data Availability

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Author Contributions

Soumitra Nath: Conceptualization; validation; visualization; writing—original draft; writing—review and editing.

Conflicts of Interest

The author declares no conflict of interest.

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