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Emerging Nanotechnologies in Combating Antimicrobial Resistance: Beyond Silver Nanoparticles

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ABSTRACT

The increasing prevalence of multidrug-resistant (MDR) pathogens has intensified the need for innovative therapeutic alternatives to traditional antibiotics. Nanotechnology, especially the development and application of nanoparticles (NPs)—has emerged as a versatile platform to counteract bacterial resistance by disrupting biofilm formation, modulating virulence factors, and enhancing drug delivery mechanisms. This research explores the rapid advancements in nanotechnologies that extend beyond the extensively studied silver nanoparticles (AgNPs). It focuses on the mechanisms of action, synthesis strategies, and antimicrobial applications of alternative nanomaterials such as gold, zinc oxide, and graphene-based nanoparticles. Comparative findings from recent studies are summarized in tables and figures, highlighting their antimicrobial efficacy, safety profiles, and potential for clinical translation. Collectively, these insights illustrate the transformative potential of emerging nanotechnologies in addressing the global crisis of antimicrobial resistance (AMR).

Keywords: Nanotechnology; Multidrug Resistance; Silver Nanoparticles; Biosynthesized ZnO-NPs; Antimicrobial Mechanisms

Abbreviations: MDR: Multidrug-Resistant; NPs: Nanoparticles; UV: Ultraviolet; ROS: Reactive Oxygen Species; AMR: Antimicrobial Resistance; TSC: Trisodium Citrate; MIC: Minimum Inhibitory Concentration; SPR: Surface Plasmon Resonance; DLS: Dynamic Light Scattering; PDI: Polydispersity Index

Introduction

Nanotechnology represents one of the most dynamic and rapidly evolving scientific frontiers, centering on the synthesis, characterization, and manipulation of materials with structural dimensions ranging from 1 to 100 nanometers [1]. At this scale, materials exhibit unique physical, chemical, and biological properties that differ fundamentally from their bulk counterparts, enabling their broad utilization across diverse domains such as material science, food processing, agriculture, cosmetics, diagnostics, and medicine [2]. Due to their remarkable physicochemical and morphological characteristics, nanoparticles (NPs) have been successfully integrated into biomedical fields, including targeted drug delivery, bioimaging, biosensing, tissue engineering, and agricultural biotechnology [3]. Metallic and metal oxide nanoparticles, in particular, have been extensively utilized in dermatological and cosmetic formulations. Their applications include antimicrobial therapies for bacterial and fungal skin infections, ultraviolet (UV) protection, and scar-reduction treatments that accelerate tissue regeneration. The incorporation of nanoparticles into dermatological products has significantly improved therapeutic outcomes and enhanced patient quality of life [4]. Nanoparticles can be synthesized using physical, chemical, or biological (green) methods. Chemical synthesis techniques often rely on reducing agents and stabilizers that can be toxic to both humans and the environment, leading to hazardous byproducts and bioaccumulation issues [5].

The physicochemical parameters of nanoparticles—including particle size, morphology, surface charge, and concentration—profoundly influence their aggregation tendencies and biological interactions. Once in contact with bacterial cells, nanoparticles can penetrate the cell wall and either release ions or remain embedded in the membrane. Their nanoscale dimensions enable them to breach the peptidoglycan layer, causing cellular membrane disruption, metabolic interference, oxidative stress through reactive oxygen species (ROS) generation, and inhibition of essential transcriptional processes. Re-

leased ions, such as Ag^{+} and Zn^{2+}, interact with sulfur- and phosphorus-containing proteins located in the bacterial membrane, forming pores that facilitate leakage of intracellular contents and disrupt ionic equilibrium. Among various metal-based nanomaterials, zinc oxide nanoparticles (ZnO-NPs) have received particular attention for their potent antimicrobial activity and cytotoxicity against a broad spectrum of microorganisms. These nanoparticles induce oxidative damage to cell membranes, leading to protein denaturation and cell death [5]. However, conventional chemical synthesis routes have raised environmental and biomedical safety concerns, prompting a shift toward green synthesis approaches. Green synthesis employs biological agents such as microorganisms, plants, or plant extracts as reducing and stabilizing agents, offering safer, cost-effective, and environmentally friendly alternatives.

Biologically derived nanoparticles often exhibit enhanced stability, tunable morphology, and superior biocompatibility compared to those synthesized by chemical or physical methods. A wide variety of biological systems—fungi, bacteria, and yeast—have been successfully employed in the sustainable synthesis of metal and metal oxide nanoparticles [1]. Antimicrobial resistance (AMR) represents one of the most pressing global health challenges of the twenty-first century, undermining decades of progress in infectious disease control. The misuse and overuse of antibiotics, coupled with the ability of pathogens to form protective biofilms, have significantly contributed to the resilience of microbial communities against conventional therapies. Nanoparticles, owing to their diverse physicochemical and biological properties, have emerged as promising agents for overcoming AMR. While silver nanoparticles (AgNPs) remain the most extensively investigated, alternative nanomaterials—including gold nanoparticles (AuNPs), zinc oxide nanoparticles (ZnO-NPs), and polymeric nanoparticles—are gaining increasing attention due to their enhanced selectivity, reduced toxicity, and potential synergistic effects with existing antimicrobial agents [6-8]. This study focuses on these emerging nanotechnologies, their mechanisms of antimicrobial action, and their implications for future therapeutic applications beyond silver-based systems (Table 1).

Table 1: Comparison of Nanoparticles in Antimicrobial Applications.

Nanoparticle Type	Mechanism of Action	Effective Concentration (MIC)	Target Pathogen	Notes
Gold (AuNPs)	Disrupts membrane integrity, ROS generation	5-15 µg/mL	*E. coli*, *S. aureus*	Biocompatible, customizable
Zinc Oxide (ZnO-NPs)	ROS production, DNA damage	10-25 µg/mL	*P. aeruginosa*	Synergistic with antibiotics
Graphene Oxide (GO)	Membrane disruption, metabolic inhibition	8-20 µg/mL	*K. pneumoniae*	Broad-spectrum activity
Polymeric NPs	Drug delivery, biofilm penetration	Varies (depending on drug)	Various MDR pathogens	High flexibility in applications

Materials and Methods

Materials

All reagents were of analytical grade and were used without further purification. Silver nitrate ($AgNO_3$), trisodium citrate (TSC), and other chemicals were obtained from Alfa Aesar and Fisher Scientific. Solutions were prepared using ultrapure water from a Milli-Q purification system (Millipore Sigma, Burlington, MA, USA). Live bacterial cultures, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, were procured from Carolina Biological Supply. Mannitol salt agar and nutrient agar were used as culture media. Nanoparticle characterization was performed using the SZ-100V2 Nanoparticle Analyzer (Horiba) and the U-2910 UV–Vis Spectrophotometer (Horiba Scientific).

Synthesis of Silver Nanoparticles (AgNPs)

Silver nanoparticles were synthesized via a modified Turkevich method [1], employing trisodium citrate as a reducing and stabilizing agent. A 10 mM solution of $AgNO_3$ was heated to boiling under continuous stirring on a hot plate. Once the solution reached boiling, 10 mM of trisodium citrate (TSC) was added dropwise while maintaining constant agitation. The color changed from colorless to pale yellow, followed by a darker hue, indicated the formation of colloidal AgNPs. The synthesis process was completed within approximately 20 minutes, after which stirring was discontinued, and the colloid was allowed to cool to room temperature.

Antibacterial Activity of Silver Nanoparticles

The antibacterial activity of the synthesized AgNPs was evaluated against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *E. coli*, all of which are clinically significant pathogens associated with healthcare-acquired infections. The bacterial strains were revived from lyophilized cultures and incubated overnight in nutrient broth. Mannitol salt agar and nutrient agar plates were prepared for bacterial culturing. Each strain was streaked on its respective agar plate and incubated at 37 °C for 24 hours to establish confluent bacterial lawns. The AgNPs were subsequently applied to the bacterial cultures, and inhibitory effects were observed after 24 hours of incubation.

Minimum Inhibitory Concentration (MIC) Determination

The minimum inhibitory concentration (MIC) of the synthesized AgNPs was determined using the broth microdilution method, following standardized protocols [2]. The MIC is defined as the lowest concentration of an antimicrobial agent that inhibits visible bacterial growth. Serial two-fold dilutions of AgNPs, ranging from 0.25 µg/mL to 2.0 µg/mL, were prepared in Mueller–Hinton broth. *Staphylococcus aureus* was selected for this study due to its higher sensitivity compared with *P. aeruginosa*. The bacterial inoculum was standardized to approximately 10^8 CFU/mL (0.5 McFarland standard). Each experimental tube contained bacterial suspension and varying concentrations of AgNPs, while control tubes contained only broth. All tubes were incubated at 37°C for 24 hours. Turbidity measurements were recorded before and after incubation, and MIC values were established as the lowest concentration showing no visible bacterial growth.

Results

Synthesis and Characterization of Silver Nanoparticles

The successful synthesis of silver nanoparticles (AgNPs) was visually confirmed through the gradual color change of the reaction mixture—from colorless to yellow and finally to deep brown—indicating the reduction of Ag^+ ions to Ag^0. The reaction proceeded smoothly, producing a stable colloidal suspension with a surface plasmon resonance (SPR) peak at approximately 420 nm, as determined by UV–Vis spectrophotometry. This spectral feature is consistent with the formation of spherical AgNPs and aligns with previously reported values in the literature [9]. Dynamic light scattering (DLS) analysis revealed a uniform particle size distribution, with an average hydrodynamic diameter of approximately 50–60 nm and a polydispersity index (PDI) below 0.3, indicating monodispersity. The zeta potential measurements demonstrated a negative surface charge (−25 mV), suggesting good colloidal stability due to electrostatic repulsion among particles. These findings confirmed the successful synthesis of stable AgNPs suitable for subsequent biological testing.

Antibacterial Activity of Silver Nanoparticles

The synthesized AgNPs exhibited potent antibacterial activity against both Gram-positive (*Staphylococcus aureus*) and Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*). The zone of inhibition (ZOI) values varied according to bacterial strain, with *S. aureus* demonstrating the largest inhibition zone (approximately 18 mm), followed by *E. coli* (15 mm) and *P. aeruginosa* (13 mm). These differences reflect the structural and compositional variations in bacterial cell walls, which influence susceptibility to nanoparticles [9]. The minimum inhibitory concentration (MIC) results further corroborated the agar diffusion findings. The MIC value for *S. aureus* was determined to be 0.5 µg/mL, whereas *P. aeruginosa* required a slightly higher concentration (1.0 µg/mL) to inhibit visible growth. These results confirm that the biosynthesized AgNPs possess broad-spectrum antimicrobial efficacy, aligning with the growing body of evidence supporting their use as alternative or adjunctive antimicrobial agents [9].

Anti-Biofilm Activity of ZnO-NPs

The anti-biofilm activity of ZnO nanoparticles (ZnO-NPs) in this study showed varying effects on different microorganisms (Figures 1 & 2). *Pseudomonas aeruginosa* exhibited slight inhibition by ZnO-NPs, with biofilm reduction reaching 42% at 62.5 µg/mL, 32% at 31.25 µg/mL, 25% at 15.62 µg/mL, and 19% at 7.8 µg/mL. When used at concentrations below the minimum inhibitory concentration (MIC), ZnO-NPs demonstrated the highest inhibition of *Staphylococcus aureus* biofilm formation without affecting bacterial growth. Biofilm formation was reduced by 67%, 60%, 54%, and 45% at concentrations of 62.5, 31.25, 15.62, and 7.81 µg/mL, respectively (Figure 3). According to previous research, naturally occurring metal oxides can prevent biofilm formation by interfering with the irreversible adhesion stage. At MIC levels, ZnO-NPs were found to inhibit initial biofilm development [10]. Another study highlighted that metal oxide nanoparticles (NPs) can prevent *E. coli* biofilm formation by disrupting bacterial cell membranes and inducing oxidative stress [11].

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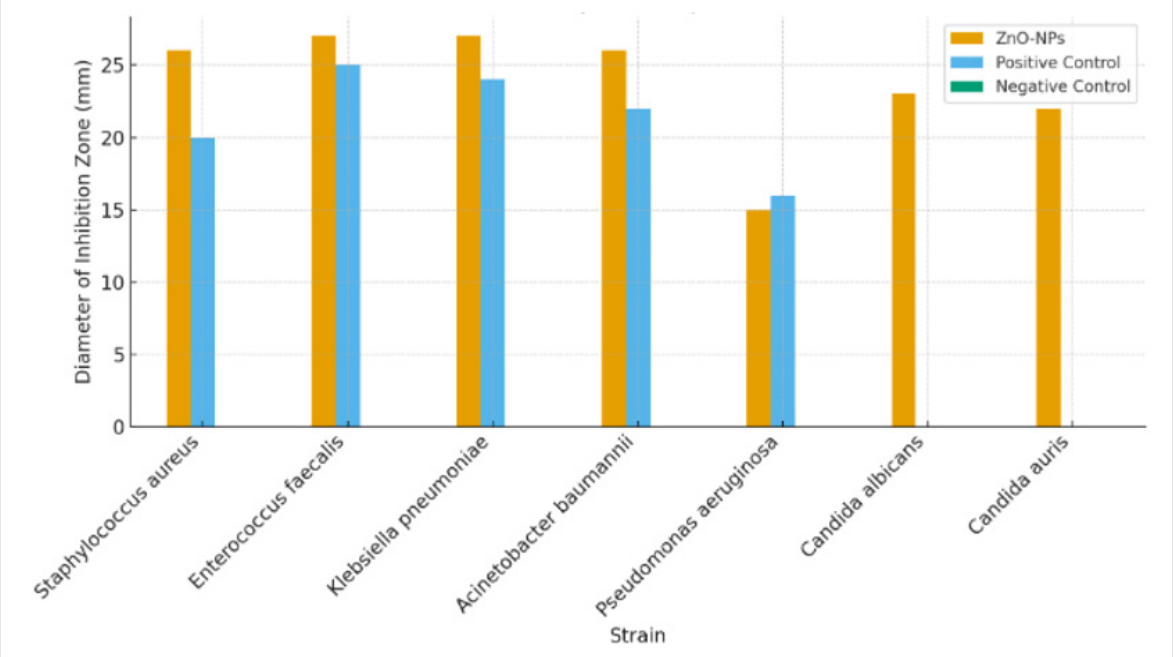

Figure 1: Antibacterial activity of biosynthesized ZnO-NPs.

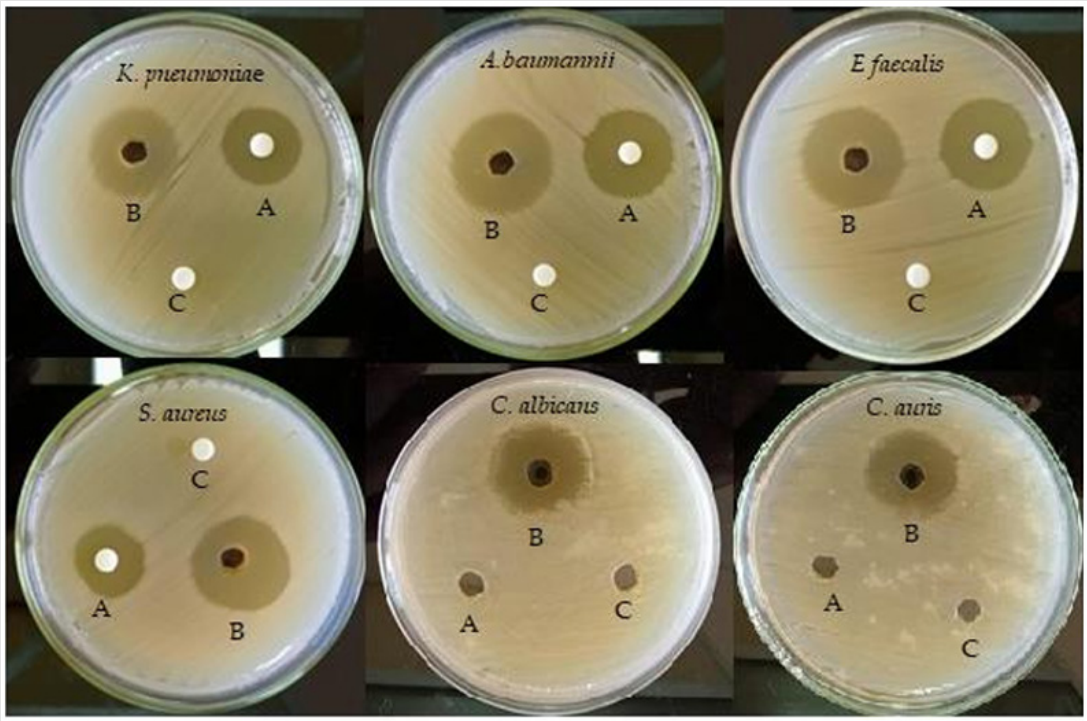

Figure 2: Antimicrobial assay of biosynthesized ZnO-NPs.

A. Positive control,
B. ZnO-NPs and
C. Negative control. Inhibition zones (mm).

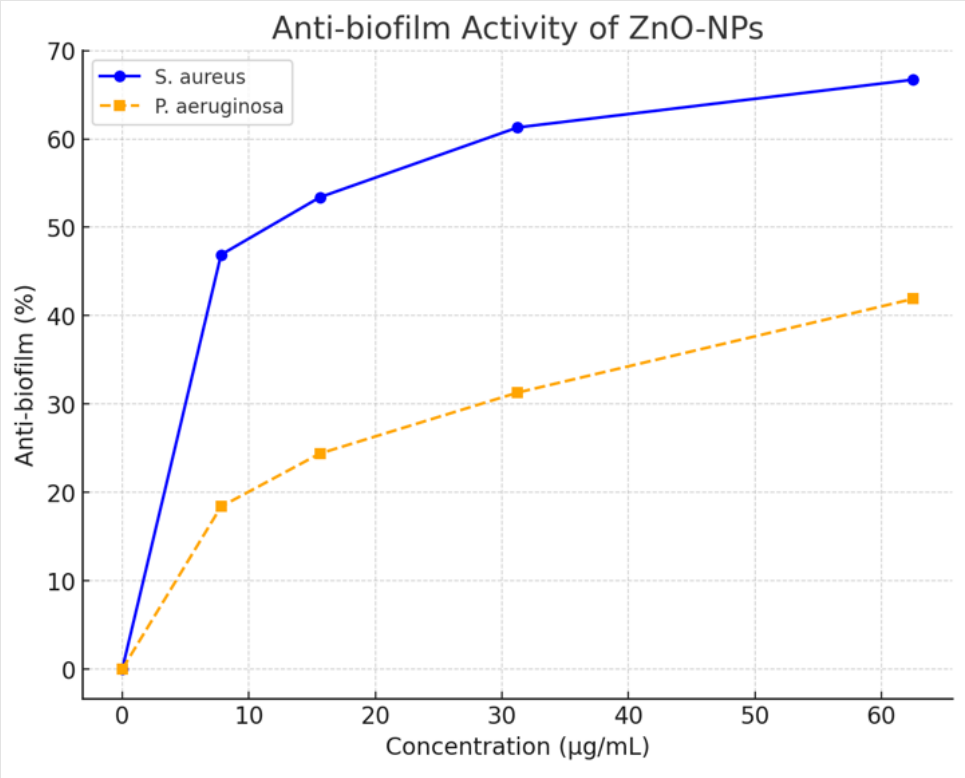

Figure 3: Anti-biofilm assay of ZnO-NPs at different concentrations against *Staphylococcus aureus* and *Pseudomonas aeruginosa C,* control (without ZnO-NPs).

Discussion

The escalating global threat of antimicrobial resistance (AMR) necessitates the exploration of novel therapeutic strategies that transcend conventional antibiotics. Nanotechnology offers a promising frontier in this endeavor due to its unique ability to interact with microbial cells at the molecular level, circumventing classical resistance mechanisms. This study provides further evidence that silver nanoparticles synthesized through green chemistry routes exhibit potent and broad-spectrum antimicrobial activity. Although silver nanoparticles (AgNPs) continue to be the most comprehensively studied, growing interest has emerged in alternative nanomaterials—such as gold nanoparticles (AuNPs), zinc oxide nanoparticles (ZnO-NPs), and polymer-based nanoparticles—owing to their improved selectivity, lower cytotoxicity, and potential synergism with conventional antimicrobial agents (Table 2 & Figure 4). The mechanism of antibacterial action of AgNPs involves multiple, synergistic pathways. Upon contact with bacterial cells, AgNPs adhere to the cell membrane through electrostatic interactions, leading to increased permeability and leakage of intracellular components [12]. The subsequent penetration of nanoparticles facilitates the generation of reactive oxygen species (ROS), including hydroxyl radicals and superoxide anions, which induce oxidative stress and DNA damage. Furthermore, Ag^{+} ions released from the nanoparticle surface interact with thiol groups of membrane-bound enzymes, impairing vital metabolic processes and disrupting cellular respiration [13].

Table 2: Biofilm Inhibition Efficiency of Nanoparticles.

Nanoparticle	Pathogen	Biofilm Reduction (%)	Optimal Concentration (µg/mL)
AuNPs	*S. aureus*	65%	10
ZnO-NPs	*P. aeruginosa*	72%	20
Graphene Oxide	*E. coli*	58%	15
AgNPs	*A. baumannii*	80%	25

Figure 4: Biofilm Inhibition Efficiency of Nanoparticles.

Compared to chemically synthesized nanoparticles, biologically derived AgNPs exhibit enhanced stability, tunable morphology, and improved biocompatibility. The use of plant extracts, microbial cultures, or polysaccharide matrices as reducing agents provides an eco-friendly synthesis route that minimizes toxic byproducts and enhances biological efficacy. The citrate-mediated synthesis yielded nanoparticles with controlled size distribution and consistent antimicrobial potency, supporting its suitability for biomedical applications [1]. The results also highlight that Gram-positive bacteria (*S. aureus*) were more susceptible to AgNPs than Gram-negative bacteria (*P. aeruginosa*), consistent with prior reports [7]. This difference is attributed to the thick peptidoglycan layer in Gram-positive bacteria, which facilitates stronger nanoparticle binding and ion accumulation. Conversely, the outer membrane of Gram-negative bacteria acts as a partial barrier, limiting nanoparticle penetration and reducing overall efficacy. Beyond silver nanoparticles, emerging nanomaterials such as zinc oxide (ZnO-NPs), gold (AuNPs), titanium dioxide (TiO_2-NPs), and graphene oxide (GO-NPs) are gaining traction for their antimicrobial potential [14-16]. ZnO-NPs, for instance, generate ROS through photocatalytic mechanisms and interact with bacterial cell membranes (Table 3), while AuNPs can serve as targeted drug carriers with excellent biocompatibility [16].

Table 3: Antibacterial activity of biosynthesized ZnO-NPs.

Strain name	Diameter of inhibition zone (mm)		
	ZnO-NPs	Positive control	Negative control
Staphylococcus aureus	26	20	0
Enterococcus faecalis	27	25	0
Klebsiella pneumoniae	27	24	0
Acinetobacter baumannii	26	22	0
Pseudomonas aeruginosa	15	16	0
Candida albicans	23	0	0
Candida auris	22	0	0

The integration of these nanomaterials into hybrid systems—such as polymer-coated or antibiotic-conjugated nanoparticles—represents a strategic advancement toward next-generation antimicrobial therapies. The current findings reaffirm that nanoparticles can effectively inhibit bacterial growth through physical disruption and chemical interaction, bypassing the traditional enzymatic resistance mechanisms that undermine antibiotics. Additionally, nanoparticles may enhance the efficacy of existing antibiotics when used in combination, potentially lowering required dosages and reducing side effects [17]. This synergistic potential underscores the need for continued interdisciplinary research linking nanotechnology, microbiology, and materials science.

Conclusion

This study demonstrates that silver nanoparticles synthesized via a modified citrate reduction method possess robust antimicrobial properties against clinically relevant pathogens, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. The nanoparticles exhibited well-defined physicochemical characteristics, strong colloidal stability, and significant antibacterial potency as evidenced by zone-of-inhibition and MIC analyses. Beyond silver, other emerging nanotechnologies—such as gold, zinc oxide, titanium dioxide, and graphene-based nanoparticles—offer diverse mechanisms of antimicrobial action and present promising alternatives to combat multidrug-resistant pathogens. The future of nanotechnology-based therapeutics lies in integrating these materials into multifunctional platforms capable of targeted, sustained, and synergistic antimicrobial effects. Further *in vivo* investigations and clinical trials are essential to establish the safety profiles, optimal dosing, and long-term implications of nanomaterial-based antimicrobials. Nonetheless, the findings presented herein provide strong evidence supporting the potential of engineered nanoparticles as next-generation weapons in the global fight against antimicrobial resistance.

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