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Review article

Harnessing nanomaterials to combat antimicrobial resistance: current advances, mechanisms, and future directions

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ABSTRACT

Antimicrobial resistance (AMR) has emerged as a critical global health concern, limiting the efficacy of conventional antibiotics and demanding novel therapeutic strategies. Nanomaterials, due to their unique physicochemical and surface properties, have demonstrated significant potential in combating AMR-associated infections, including those caused by multidrug-resistant (MDR) pathogens. This review evaluates the antimicrobial performance of various nanomaterials, including metal and metal oxide nanoparticles (Ag, ZnO, TiO_2), carbon-based nanomaterials, polymeric systems, lipid-based carriers, and quantum dots. Experimental studies report that Ag and ZnO nanoparticles can achieve up to 95% bacterial reduction at concentrations below 50 μg/mL, while nanocomposite systems (i.e., multi-component or matrix-supported materials) enhance antibiotic efficacy by 3–5-fold. The mechanisms responsible for these effects such as reactive oxygen species (ROS) generation, membrane disruption, inhibition of biofilm formation (>80%), and genetic modulation are discussed in detail (with emphasis on antibacterial models and endpoints). The review also examines the emergence of microbial resistance to nanomaterials, highlighting adaptive responses including efflux pump activation and biofilm-associated resistance. Challenges hindering clinical translation, particularly cytotoxicity, biocompatibility, and scalability, are critically analyzed. Finally, recent advances in the development of smart and stimuli-responsive nanomaterials, and their integration with artificial intelligence and vaccine technology, are presented as promising future directions. This review provides a scientific overview of current progress, challenges, and perspectives in applying nanomaterials to mitigate AMR and facilitate their transition from laboratory research to clinical implementation.

1. Introduction

Antimicrobial resistance (AMR) has emerged as one of the most critical global health challenges of the 21st century, exerting a profound burden on healthcare systems, economies, and societies worldwide (Ahmed et al., 2024; Muteeb et al., 2025; Salam et al., 2023). In 2019, AMR was directly responsible for approximately 1.27 million deaths, with an even greater number of fatalities associated with resistant

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infections, and current projections warn that if decisive interventions are not implemented, AMR-related deaths could soar to 10 million annually by 2050 (Murray et al., 2022). AMR arises when microorganisms including bacteria, fungi, viruses, and parasites acquire or evolve mechanisms that render antimicrobial agents ineffective (Muteeb et al., 2025). These mechanisms are diverse and complex, encompassing genetic adaptations such as spontaneous mutations, horizontal gene transfer via plasmids and transposons, and biochemical strategies like enzymatic degradation of antibiotics, activation of efflux pumps, alteration of drug targets, and formation of protective biofilms (Muteeb et al., 2023; Salam et al., 2023). Although significant strides have been made in antibiotic discovery and development over the past century, the escalating prevalence of multidrug-resistant (MDR) pathogens, coupled with the dwindling pipeline of new antimicrobial agents, has rendered conventional therapeutic approaches increasingly ineffective. The imbalance between the pace of resistance emergence and the slow approval of novel antibiotics underscores the urgent and unmet need for innovative strategies to combat AMR (Nwobodo et al., 2022; Muteeb et al., 2023).

Nanotechnology, defined as the manipulation and control of materials at the nanoscale (1–100 nm), has revolutionized the field of medicine by offering unprecedented opportunities for diagnosis, treatment, and prevention of diseases (Malik et al., 2023). Engineered nanomaterials exhibit unique physicochemical properties such as high surface-area-to-volume ratios, quantum effects, and tunable surface functionalities that are absent in their bulk counterparts (Kurul et al., 2025; Sohail, 2025). These distinctive features confer several therapeutic advantages over traditional antimicrobial therapies, including enhanced penetration of biological barriers, targeted delivery to infected tissues, improved bioavailability, and multifunctionality, such as the simultaneous exertion of antimicrobial, anti-inflammatory, and immunomodulatory effects (W. Xiao et al., 2025). Furthermore, the surface chemistry of nanomaterials can be tailored to enable the co-delivery of therapeutic agents and imaging probes, facilitating integrated theragnostic applications (Kaymaz et al., 2023). Crucially, nanomaterials have demonstrated remarkable efficacy in models of AMR-associated infection, including infections caused by MDR pathogens through innovative mechanisms of action, including physical disruption of microbial membranes, induction of ROS leading to oxidative stress, and inhibition of biofilm development, positioning them as a highly promising frontier in the fight against AMR (Aflakian et al., 2023).

Considering the growing threat of AMR and the limitations of current therapies, this review offers a timely and distinctive synthesis of the emerging role of nanomaterials as next-generation therapeutics against resistant infections. While previous reviews have largely summarized the antimicrobial activities of nanomaterials, the novelty of this work lies in its integrative and mechanism-driven approach that links material design principles directly to clinical translation challenges. Specifically, this review uniquely combines: (i) a comparative evaluation of nanomaterial classes based on their structure–activity relationships, (ii) an in-depth discussion of molecular and cellular mechanisms underlying antimicrobial action, and (iii) a critical assessment of toxicity, biosafety, and regulatory constraints that influence clinical applicability. By bridging fundamental mechanistic insights with real-world translational considerations, this review not only consolidates current knowledge but also establishes a forward-looking roadmap for designing safer and more effective nanomaterial-based antimicrobial agents. This dual mechanistic–translational perspective clearly differentiates our review from existing literature and underscores its contribution to guiding future research directions in combating antimicrobial resistance.

This review follows a materials-to-mechanisms-to-translation logic: First, key antimicrobial nanomaterial platforms are classified (Section 2.1), their therapeutic applications are summarized (Section 2.2), mechanistic bases of antimicrobial activity and resistance-relevant pathways are explained (Sections 3–4), and finally translational barriers and future directions are evaluated (Sections 5–7). Throughout this review, "antimicrobial" is used as an umbrella term; however, unless explicitly stated otherwise (e.g., antifungal formulations such as amphotericin B), the discussion and performance metrics (e.g., MICs, MRSA, Gram-positive/Gram-negative models) primarily reflect antibacterial activity.

2. Nanomaterials for combating AMR: current advances

Nanomaterials can help overcome the antibiotic-resistance mechanisms because their unique physiochemical properties enable multiple novel microbicidal pathways to operate simultaneously. For example, many nanomaterials interact directly with bacterial membranes, causing structural disruption and leakage of intracellular contents. Specifically, nanoparticles (NPs) have recently emerged as promising tools to combat deadly drug-resistant infections, particularly bacterial infections, which are primary focus of this review. Compared with traditional antimicrobials, nanoparticle-based strategies offer opportunities to bypass permeability barriers, enhance local drug concentration, and integrate multiple modes of action within a single platform. This section provides an overview of the different classes of functional nanomaterials used in AMR-related therapeutics. Section 2 first outlines the main classes of antimicrobial nanomaterials (Section 2.1) and then summarizes how these platforms are applied in antimicrobial therapy (Section 2.2), thereby following a materials-to-applications progression.

2.1. Types of nanomaterials used against AMR

2.1.1. Metal and metal oxide nanoparticles

Nanoparticles are small particles with dimensions within the range of 1–100 nm, and they constitute a sub-class of nanomaterials (Boverhof et al., 2015; Jeevanandam et al., 2018). Nanoparticles are of the different types, forms, and shapes but metal and metal-oxide types receive more attention owing to their relevance in the design of antimicrobial drugs (Dizaj et al., 2014). In particular, metal nanoparticles (NPs) such as silver (Ag), gold (Au), and copper (Cu) and metal oxide NPs like zinc oxide (ZnO) and copper oxide (CuO), have been extensively explored as antimicrobials. Ag and Au nanoparticles typically contain relatively few metal atoms (often 5–100 nm in size) and are generally synthesized by chemical reduction of respective metal ions (Ag^{+} or Au^{3+}) by a reducing agent with(out) a capping agent for their surface functionalization (Moradi et al., 2023). ZnO and CuO NPs are crystalline metal oxides (often $<$50 nm) made by precipitation or hydrothermal methods; at the nanoscale they exhibit enhanced surface reactivity and photocatalytic properties (Melese et al., 2025; Nguyen et al., 2023).

The chemical reduction methods for AgNPs are readily scalable to industrial production (some commercial products already use nanocrystalline silver), while high-quality shape-controlled AuNPs or doped metal oxides may require more complex synthesis, affecting large-scale cost. Nonetheless, significant progress has been made in scalable "green" synthesis for Ag and Au NPs, and spray pyrolysis or wet chemical methods for ZnO/CuO are industrially feasible (Abdel-Raouf et al., 2017; Ying et al., 2022). The crucial properties of these NPs include their high surface-area-to-volume ratio and tunable surface chemistry, which allow these NPs to interact strongly with microbial cells. For example, Ag and Cu NPs can release ions (Ag^{+}, Cu^{2+}) and generate reactive oxygen species (ROS) under physiological conditions while ZnO NPs can be activated by UV/visible light to produce ROS (Rashid et al., 2024).

With recent advances in science in the last decade, atom-precise NPs of these noble metals are being synthesized and extensively characterized with state-of-the-art technology. Achieving precise control over size and shape enables maximizing their antimicrobial activity. For instance, smaller AgNPs (~10 nm) show significantly higher antibacterial potency than larger ones, as they more readily attach to and penetrate bacterial membranes (Lalsangpuii et al., 2022; Vanlalveni et al., 2024).

In another study, truncated triangular Ag nanoplates reportedly exhibit superior bactericidal effects compared to spherical or rod-shaped AgNPs, because the triangular plates expose more facets for interacting with bacterial surfaces, causing greater membrane damage (Fig. 1). These examples distinctly highlight the size- and shape-dependency effect of these NPs (Nam et al., 2015). More so, the advances in green synthesis, with the use of biological extracts, have improved the scalability and eco-friendliness of AgNP production (Fahim et al., 2024). Au NPs have also seen progress as photothermal agents and drug carriers. For example, Au nanorods can convert near-infrared light to heat to kill bacteria, and ultrasmall Au clusters have been loaded with antibiotics to create synergistic nano-antibiotics (Amaral et al., 2025).

Generally, metallic NPs generally exhibit broad-spectrum antimicrobial effects, effective against Gram-positive and Gram-negative bacteria and even fungi. While Ag NPs often achieve complete growth inhibition at low μg/mL concentrations (Correa et al., 2020), Au NPs typically require functionalization (e.g. with antimicrobial peptides or antibiotics) to reach comparable potency (Sa'ed et al., 2024). ZnO and CuO NPs are effective particularly under conditions that promote ion release or ROS generation (e.g. acidic pH or light exposure) (Melese et al., 2025). In terms of colloidal stability, uncoated AgNPs may aggregate in biological media, reducing efficacy, but polymer or protein capping agents are used to stabilize dispersions and prolong activity (Sati et al., 2025). For metal oxides, researchers have developed doped and defect-engineered ZnO NPs that generate ROS even in the dark, enhancing antibacterial efficacy (Okeke et al., 2022). ZnO NPs are generally stable solids, but their antibacterial activity can diminish if their surfaces become passivated (e.g. by proteins adsorbing in serum). Nanoscale CuO has been combined with other materials (e.g. on graphene oxide supports) to improve stability and allow controlled Cu^{2+} release for long-term antimicrobial action (Gaikwad et al., 2026).

Globally, several research groups drive advances in metal nanomaterials for AMR. Huma et al. (2018) reported surface-functionalized AgNPs that selectively target bacteria and evade resistance. Proteomic studies have been used to elucidate the antibacterial mechanisms of AgNPs (Yan et al., 2018), while parallel work has highlighted AuNPs as promising "magic bullet" platforms against multidrug-resistant bacteria because of their biocompatibility and ease of functionalization (Okkeh et al., 2021). This global network of researchers has significantly advanced the state-of-the-art of metal-based nano-antimicrobials. It is also noteworthy that the last decade has also witnessed significant progress in the design and synthesis of bimetallic NPs (Ag/Cu, Ag/Au, etc.) with enhanced antimicrobial performance via multiple concurrent mechanisms (Malik et al., 2023).

A critical consideration for metal and metal oxide NPs is toxicity to human cells and the environment. Ag NPs are highly effective but can induce cytotoxicity at higher doses by causing oxidative stress and inflammation in human cells (Manuja et al., 2021). Careful surface

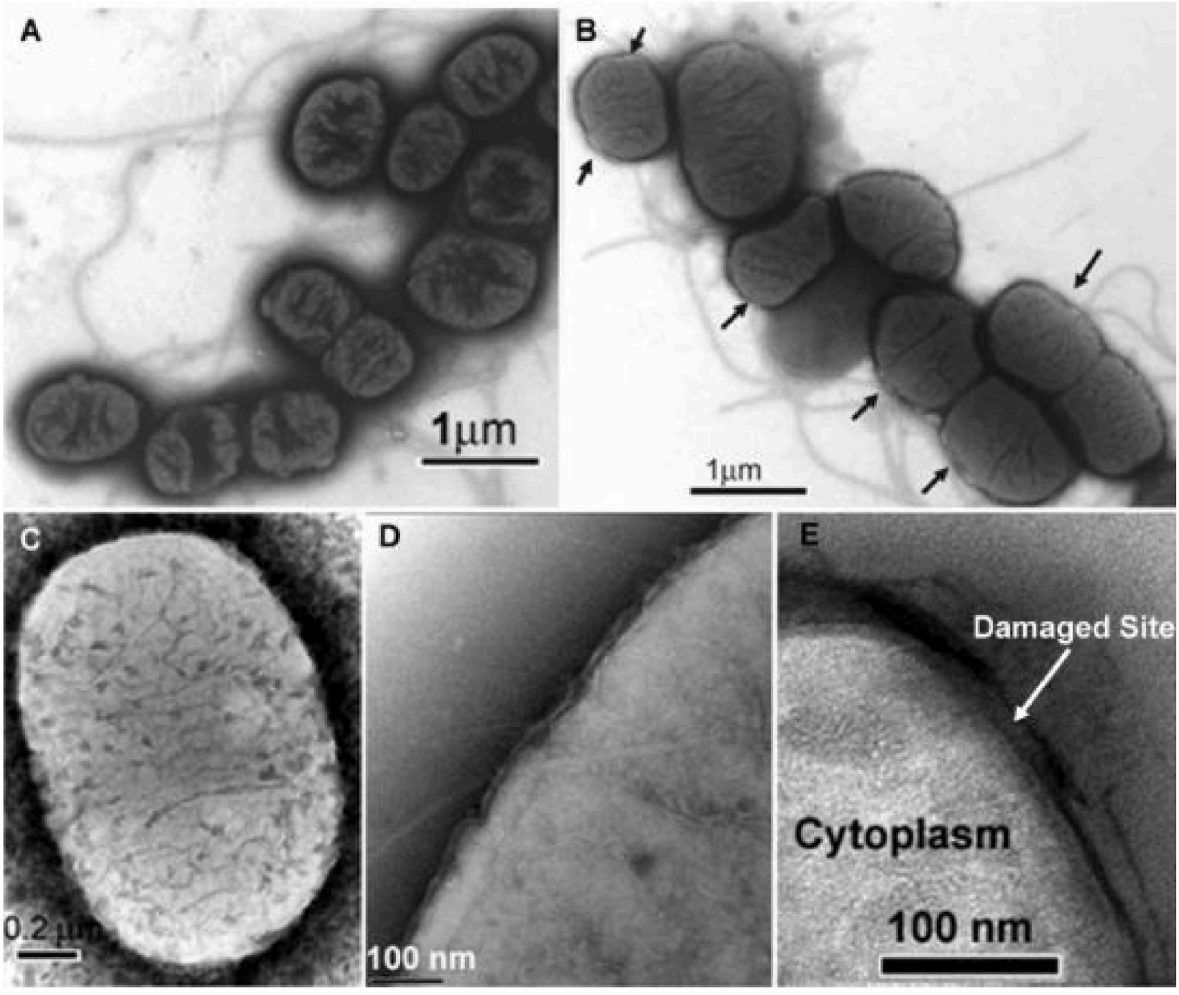

Fig. 1. EFTEM images of *E. coli* cells. (A) Untreated *E. coli*. Flagella can be seen. (B) *E. coli* grown on agar plates supplemented with Ag^{+} ($AgNO_3$). Arrows indicate partially damaged membranes. These cells are viable. (C) *E. coli* treated with triangular silver nanoplates. Silver nanoparticles appear as dark irregular pits on the cell surface. (D) *E. coli* treated with spherical silver nanoparticles. (E) Enlarged image of part of the bacterial cell membrane treated with triangular silver nanoparticles. The cell membrane is damaged in multiple locations. Reprinted from Nam et al., (2015), licensed under CC BY 3.0 (https://creativecommons.org/licenses/by/3.0/).

engineering (e.g. coating AgNPs with biocompatible polymers) can mitigate this, as demonstrated by polymer-coated AgNPs that killed bacteria by disrupting metabolism while reducing host toxicity (Laib et al., 2025). Au NPs are generally considered more biocompatible – they are often well tolerated *in vivo*, especially when coated with inert shells (e.g. PEG). However, since pristine AuNPs only have mild antimicrobial action (Kang et al., 2020), their safety profile remains favorable when used as carriers or photothermal agents. ZnO is considered safe in certain uses; it is even used in sunscreens, but nano-ZnO can dissolve releasing Zn^{2+}, which in excess may harm human cells. Fortunately, ZnO's threshold of toxicity is higher for human cells than for bacteria, offering a therapeutic window. CuO NPs release Cu^{2+}, which can be toxic to mammalian cells at high concentrations and have been associated with oxidative damage to liver cells in some studies. Thus, CuO use may be preferable in topical or surface applications rather than systemic.

Overall, while metallic nanomaterials sidestep many bacterial resistance mechanisms, their deployment must balance antimicrobial potency with biocompatibility. Ongoing research is evaluating safe dose ranges, long-term accumulation (e.g. argyria from silver), and strategies like targeting moieties to confine NPs to infection sites (Liao et al., 2025). Importantly, bacteria have difficulty developing genetic resistance to the multifaceted attacks of metal NPs, but some adaptive responses (like biofilm encasement or efflux of metal ions) can occur. Thus, careful design and thorough toxicity testing are mandatory for clinical translation of metal-based nano-antimicrobials.

2.1.2. Carbon-based nanomaterials

Aside metal and metal-oxide NPs, carbon-based nanomaterials such as graphene oxide (GO), carbon nanotubes (CNTs), and fullerenes are also employed against AMR. GO is a single-atom-thick sheet of carbon lattice decorated with oxygen-containing groups (epoxide, hydroxyl, carboxyl). Its sharp edges and large surface area enable direct contact with microbial membranes, potentially slicing or wrapping bacteria (Singh et al., 2024). In fact, GO exhibits strong antimicrobial effects primarily via contact-mediated membrane disruption and oxidative stress. Even at concentrations in the low tens of μg/mL, GO can inhibit bacterial growth and biofilm formation, and studies have shown that GO sheets can be engineered to optimal size/thickness for microbial capture and membrane perturbation (Singh et al., 2024). Its efficacy is influenced by lateral size (smaller GO sheets penetrate cell membranes more easily, whereas very large sheets may be less effective but can act as coating materials). Reduced GO (with fewer oxygen groups) offers higher conductivity and has been used in photothermal therapy; under infrared light, rGO heats up and kills bacteria within biofilms (Zhang et al., 2019).

Graphene oxide is reasonably stable in dry form and can be produced in bulk by oxidation of graphite (Hummers' method), making it scalable; however, in physiological fluids GO tends to aggregate unless well functionalized. Several research groups have studied how GO functionalization affects bacterial membrane interactions (Marsala et al., 2025). GO can be functionalized with silver nanoparticles or quaternary ammonium groups, combining GO's mechanical disruption with chemical killing (Derakhshi et al., 2018). Graphene oxide at high concentrations or large sheet sizes can induce oxidative stress and physical damage in mammalian cells (especially to cell membranes and lungs if inhaled), but at controlled sizes and doses GO can be biocompatible (Zhang et al., 2021). Surface functionalization (e.g. with polyethylene glycol or other polymers) greatly improves GO's biocompatibility by reducing its sharp-edge effects and preventing aggregation that could embolize vessels. A breakthrough was the development of graphene-based nanocomposites (supported systems) – for example, immobilizing Ag or ZnO NPs onto GO sheets to achieve synergistic antibacterial effects (physical disruption from GO plus ion/ROS release from the supported nanoparticles (J. Xiao et al., 2025).

CNTs are tubular carbon structures (single- or multi-walled) with high aspect ratio; they can puncture bacterial cell walls like nanoscale spears. CNTs historically raised red flags due to their fiber-like shape (drawing parallels to asbestos); long, rigid CNTs can indeed cause inflammation or granulomas in lungs. Current approaches use shorter or functionalized CNTs, which are more readily cleared or even enzymatically broken down. Many studies show that properly functionalized, purified CNTs do not cause significant cytotoxicity at bactericidal doses (Bonner, 2011), though caution is warranted for *in vivo* use (e.g. avoid injecting long CNTs intravenously). CNTs are often functionalized with cationic polymers or peptides to improve water dispersibility and promote electrostatic binding to bacteria. CNT research has produced anti-biofilm CNT coatings, where CNT meshes on surfaces prevent bacterial attachment and kill microbes on contact (the CNT network mechanically ruptures cell membranes) (Teixeira-Santos et al., 2021).

There have also been advances in making CNTs biodegradable or safer (e.g. enzymatically degradable linkers in CNT-based materials) to address concerns of persistence and toxicity. CNTs have demonstrated bactericidal activity (especially multi-walled CNTs against Gram-negatives) but their dispersal in aqueous media is a challenge – surfactants or polymer wrapping are used for stabilization. When properly dispersed, CNTs can achieve significant bacterial killing at low concentrations by piercing cell walls (Saleemi et al., 2022). Stability of CNT suspensions can be an issue (they may settle or bundle), but surface functionalization (e.g. with DNA or polymers) has improved their colloidal stability.

Fullerenes (e.g. C_60) are spherical cages of carbon ~1 nm in diameter; by themselves they have limited solubility but can generate ROS under light or act as carriers (G. Zhang et al., 2023). Fullerenes have been modified to fullerene derivatives (e.g. functionalized with hydrophilic or cationic groups) that can produce singlet oxygen under illumination, acting as nano-photosensitizers. These structural modifications not only improve solubility but also introduce specific antimicrobial functionalities (e.g. targeting ligands or enhanced ROS production). Fullerenes by themselves have moderate antimicrobial action, often requiring light activation or combination with other agents. They are quite stable chemically (resisting degradation), which is a double-edged sword: it ensures long-lasting action but raises concerns about environmental persistence.

Fortunately, newer fullerene-polymer conjugates are being designed to be more biodegradable. Fullerenes are relatively inert to human cells in the dark, but their tendency to accumulate in cell membranes can cause membrane perturbation at high concentrations. Functionalized fullerenes (like amino-fullerenes) exhibit improved water solubility and lower cytotoxicity, making them more suitable for biomedical use. Additionally, a new class of carbon nanodots (1–10 nm “carbon quantum dots”) has emerged as effective antimicrobial agents; these fluorescent carbon dots can be tailored with surface functional groups and have shown potent antibacterial (and, in selected reports, antiviral) activity with low cytotoxicity (Goodarzi et al., 2017).

A notable advantage of carbon-based nanomaterials is that they often do not release toxic ions (unlike heavy metal NPs). However, they can generate ROS, which, while killing bacteria, might also damage host cells if not controlled. Therefore, strategies like using external triggers (light) ensure ROS generation occur primarily in the presence of target microbes. In summary, carbon-based nanomaterials can be engineered for biocompatibility, but careful dose control and thorough toxicological evaluation are needed. So far, their use *in vivo* has been mostly exploratory (e.g. GO in wound dressings or as coatings, where systemic exposure is limited). The immune response to graphene or CNTs is an area of active research; interestingly, some reports suggest graphene oxide can modulate macrophage behavior to a pro-inflammatory state that helps clear infections, but this immune activation must be balanced to avoid tissue damage. As research continues, the goal is carbon nanomaterials that maximize microbial destruction while remaining harmless to the host.

2.1.3. Polymer-based nanomaterials

Polymeric nanomaterials encompass a broad family of nano-sized constructs made from organic polymers, many of which are being harnessed to combat antimicrobial resistance. A key distinction in polymeric systems is biodegradable vs. non-biodegradable polymers. Biodegradable polymers (like PLGA – poly(lactic-co-glycolic acid), chitosan, or poly(ε-caprolactone)) will break down in the body to nontoxic byproducts, which is ideal for transient antimicrobial therapy (Kamaly et al., 2016). Non-biodegradable polymers (like some high-generation dendrimers or polyethyleneimine) persist unless excreted, which can be useful for long-term coatings but raises concerns for accumulation. The recent years witnessed the use of polymeric nanoparticles to co-deliver multiple therapeutics (like an antibiotic plus a quorum-sensing inhibitor in the same nanoparticle) to tackle resistant infections from multiple angles (Ghawanmeh, 2024). The key categories of polymeric nanomaterials include dendrimers, polymeric micelles, and nanogels.

Dendrimers are highly branched, tree-like macromolecules (typically <15 nm) with densely packed surface functional groups. For antimicrobial applications, cationic dendrimers (e.g. poly(amidoamine) – PAMAM dendrimers) are of great interest because their positively charged surface can mimic antimicrobial peptides, binding to and disrupting bacterial membranes (Fadaei et al., 2025). Each generation of a dendrimer increases its size and number of surface groups, allowing fine-tuning of its interactions and payload capacity. Dendrimers such as PAMAM or peptide dendrimers have demonstrated low micromolar or nanomolar minimum inhibitory concentrations (MICs) against resistant strains by themselves (Avila et al., 2025). Some dendrimers are bacteriostatic on their own but become bactericidal when combined with antibiotics (by helping antibiotic uptake). Their efficacy often correlates with their generation and surface charge: higher-generation cationic dendrimers can be more potent but also more toxic.

Recent work has also produced peptide-mimetic dendrimers that show potent activity against multidrug-resistant bacteria. For example, structurally nanoengineered antimicrobial peptide polymers (SNAPPs) are star-shaped peptide dendrimers that can disrupt all bacterial envelope layers (Ramamurthy et al., 2021). SNAPP dendrimers cause membrane channels and ion efflux in Gram-negatives, leading to cell lysis *in vitro* and improving survival in infection models (de Oliveira et al., 2024). Advances in dendrimer synthesis now enable attachment of targeting ligands (e.g. bacterial lipopolysaccharide-binding groups) to direct them to infection sites.

Polymeric micelle systems have also shown the ability to restore the activity of antibiotics against resistant bacteria. For example, Gaurav et al. (2023) encapsulated an efflux pump-substrate antibiotic in a stealth micelle, thereby bypassing bacterial efflux and restoring antibiotic activity in resistant *P. aeruginosa*. Polymeric micelles are self-assembled colloidal nanoparticles (10–100 nm) formed by amphiphilic block copolymers in water. They typically have a hydrophobic core (that can load hydrophobic antibiotics) and a hydrophilic shell that stabilizes them in biological fluids (Cho et al., 2025). Micelles act as nanocarriers, improving the solubility and delivery of antimicrobial drugs. Micelles are generally more about enabling antibiotic therapy than killing on their own; their stability in bloodstream (avoiding premature drug release or disintegration) is crucial. By tuning polymer composition, micelles can be made stable enough to circulate and yet, destabilize under target conditions (e.g. low pH).

Scalable manufacturing of polymeric micelles is feasible via self-assembly processes, which are like pharmaceutical liposome production techniques. Several researchers have successfully loaded a variety of antibiotics into micelles to overcome solubility or resistance issues. For instance, polymyxin antibiotics (which are effective but toxic) have been encapsulated in PEG-PLA micelles to reduce renal toxicity while retaining activity against Acinetobacter infections. Micelles have also been made stimulus-responsive, e.g. pH-responsive micelles that destabilize in acidic infection microenvironments to release their antibiotic cargo (Bintang et al., 2025).

Nanogels are soft, hydrogel nanoparticles composed of crosslinked polymer networks swollen with water (usually tens to hundreds of nm). They can be designed to encapsulate antibiotics or enzymes and release them in response to stimuli (pH, temperature, etc.), and their high water-content can improve biocompatibility. Nanogels have shown strong efficacy in localized infection models; for example, nanogel-based wound dressings achieve continuous antimicrobial release and prevent biofilm regrowth better than conventional ointments (Keskin et al., 2021). They are inherently stable as crosslinked networks (not prone to easily falling apart), and their water content can be as high as 90%, making them resemble biological tissues. Scalability for nanogels and dendrimers can be more challenging: dendrimer synthesis is a multistep process that is costly at large scale, though newer convergent synthetic methods and even biologically synthesized dendrimers are being studied.

Nanogels can potentially be produced by polymerization in emulsion at larger volumes. One advantage is that many polymer nanomaterials use FDA-approved materials (PLGA, PEG, chitosan), smoothing the path to clinical translation. There have been exciting developments in enzymatically-responsive nanogels for infectious sites – e.g. a nanogel that stays intact in circulation but is degraded by bacterial enzymes (like gelatinases or beta-lactamases) at the infection site, thus releasing antibiotics exactly where needed (Keskin et al., 2021). Temperature-responsive nanogels loaded with antibiotics have been tested for wound infections: they remain liquid at room temperature for easy application, but solidify into a gel at body temperature, slowly releasing drug into the wound. Another breakthrough is dual function nanogels that not only deliver antibiotics but also exert intrinsic antibacterial activity; for example, a nanogel made of a cationic polymer can disrupt biofilms and concurrently release a carried antibiotic, yielding complementary physical (membrane/biofilm disruption) and pharmacological (drug) effects.

Polymeric nanomaterials can be highly effective, especially as adjuncts that improve antibiotic delivery. However, they are often lauded for their biocompatibility, especially when made from biodegradable or bioinert components. For example, PLGA and chitosan-based systems degrade into lactic/glycolic acid and glucosamine, respectively, which the body can naturally metabolize. As a result, PLGA antibiotic nanoparticles have been tested in humans (for other indications) with good safety records. Dendrimers, on the other hand, require careful design: high-generation unmodified PAMAM dendrimers are known to cause membrane disruption in human cells (hemolysis) due to their high positive charge. To mitigate this, researchers use strategies like partial surface acetylation or PEGylation of dendrimers to reduce toxicity while retaining antimicrobial function (Kheraldine et al., 2021).

Many antimicrobial dendrimers are also rapidly bactericidal, which can allow for lower doses and reduced exposure to host tissues. Polymeric micelles generally use biocompatible shells (e.g. PEG), which makes them quite non-immunogenic and non-toxic; the toxicity mostly relates to the loaded drug (e.g. if the antibiotic itself is toxic). Nanogels made of materials like hyaluronic acid or dextran are usually biocompatible and even bio-adhesive, aiding wound healing. One example is a micellar polymer (Dextran-poly(AMPTMA-co-BMA)) that forms a bactericidal core with a dextran shell, which was used to treat wound biofilms without damaging mammalian cells (Kheraldine et al., 2021). Overall, polymeric nano-systems can reduce the systemic toxicity of antibiotics by concentrating the drug at the infection site and lowering needed doses (Birk et al., 2021). Importantly, many polymer nanocarriers can be designed to avoid triggering inflammation. Stealth coatings (PEG) and targeting moieties limit off-target interactions. Overall, polymer-based nanomaterials offer a high degree of tunability to maximize compatibility, and many are built from well-known pharmaceutical excipients, providing confidence in their safety profile as we advance towards clinical use.

2.1.4. Lipid-based nanomaterials

Lipid-based nanomaterials, notably liposomes and solid lipid nanoparticles (SLNs), are widely used in drug delivery and have been adapted for antimicrobial applications. Liposomes are spherical vesicles consisting of one or more phospholipid bilayers surrounding an aqueous core. They range from ~50 nm to several microns (though typically 100–200 nm for injectable formulations). Liposomes can encapsulate hydrophilic drugs in their core and hydrophobic drugs within the lipid bilayer, offering a versatile vehicle for antibiotics (Makhlouf et al., 2023). Their lipid composition (often phosphatidylcholine, cholesterol, etc.) makes them biocompatible and capable of fusing with biological membranes. Solid lipid nanoparticles (SLNs) are sub-200 nm particles made from lipids that are solid at body temperature (e.g. glyceryl stearate, triglycerides).

Unlike liposomes, SLNs are a solid matrix (often stabilized by emulsifiers), in which drugs can be embedded. Both liposomes and SLNs provide a means to improve drug solubility, protect drugs from degradation, and modulate release profiles. A major advantage of lipid-based NPs is their ability to encapsulate existing antibiotics and deliver them more effectively: e.g. encapsulating rifampicin or amphotericin B in liposomes can reduce drug toxicity and target delivery to infection sites (amphotericin B is an antifungal example) (Kapoor et al., 2025). These systems also inherently mimic biological membranes, which can facilitate uptake by cells or biofilm penetration.

Lipid-based nanocarriers have proven efficacy in enhancing antibacterial therapies. Liposomal formulations of antibiotics often show equal or improved bacterial killing *in vitro* compared to free drug, but with the benefit of improved pharmacokinetics *in vivo*. For instance, a liposomal gentamicin showed the same MIC against *P. aeruginosa* as free gentamicin, but in a lung infection model it cleared bacteria much more effectively due to higher drug retention in the lungs (Rukholm et al., 2006). Lipid NPs are especially valuable against intracellular pathogens: they can facilitate uptake of antibiotics into macrophages, thus reaching bacteria like Salmonella or Mycobacterium that hide inside host cells (Wang et al., 2023). Stability-wise, modern liposomes can be lyophilized (freeze-dried) for long-term storage and rehydrated before use, which solves earlier shelf-life issues. They are generally stable in the bloodstream for hours if PEGylated; uncoated liposomes may be cleared faster by the immune system. SLNs tend to be very stable colloids; however, a common issue known as “polymorphic transition” can cause the solid lipid to change form and expel drug over time. Researchers mitigate this with optimized lipid mixtures and surfactants.

Scalability is a strong suit of lipid nanomaterials; pharmaceutical companies have decades of experience producing liposomal drugs (e.g. liposomal amphotericin B, Doxil®, etc.). High-pressure homogenization and microfluidic mixing are techniques already used to produce LNPs at industrial scale. The recent deployment of mRNA vaccines in LNPs means there is large manufacturing capacity for lipid nanoparticles, which can potentially be leveraged for antibacterial formulations as well. One challenge can be cost, as some specialty lipids and scaling processes are expensive, but the technology is mature relative to other nanomaterials.

Lipid-based nanoparticles are among the most biocompatible delivery systems available. Because they are made of lipids like those in cell membranes (phosphatidylcholine, etc.), the body tolerates them well. Liposomes can fuse with cell membranes or be taken up by endocytosis without triggering severe immune reactions (especially if “stealth” with PEG to avoid complement activation). Toxicity is usually low – for example, the dose-limiting toxicity of liposomal amphotericin B is much lower than free amphotericin's, as the liposomal form avoids interactions with human cell membranes that cause side effects. One must consider the payload toxicity: liposomes can reduce off-target effects of toxic antibiotics, but if the liposome releases a large burst of drug in one spot, local toxicity could occur. Solid lipid nanoparticles use biocompatible lipids (often even edible-grade fats), and in toxicity studies they generally show minimal issues; indeed, some SLNs have been evaluated for IV injection with good safety (Islam et al., 2025; Yusuf et al., 2023).

A potential concern with lipid NPs is the use of cationic lipids (sometimes included to facilitate binding to negatively charged bacterial surfaces or nucleic acid delivery). Cationic lipids (like DOTAP, DOTMA) can be cytotoxic and pro-inflammatory at high concentrations, causing cell membrane disruption or triggering cytokine release. However, antimicrobial LNP formulations often either avoid strongly cationic lipids or use them in small fractions, balancing efficacy and safety (Wang et al., 2023). The biocompatibility of lipid systems is underscored by their regulatory approvals: multiple liposomal formulations are FDA-approved (for cancer, fungal infections, and recently, vaccines), and their safety is well documented.

Another consideration is immune system interactions; repeated injections of liposomes can sometimes provoke accelerated blood clearance or mild immune reactions, but this is formulation-dependent (Dams et al., 2000). For local use (e.g. inhaled or topical delivery), lipid NPs have shown favorable tolerability; for example, inhaled amikacin liposome formulations enable high pulmonary drug exposure while minimizing systemic exposure relative to intravenous amikacin (Shirley, 2019). In summary, lipid-based nanomaterials are generally safe carriers that can actually reduce the overall toxicity of antibacterial treatments by improving targeting. Ensuring that their components (lipids, stabilizers) are pharmaceutical grade and non-immunogenic is key, and ongoing research is refining lipid compositions for optimal safety/efficacy in antimicrobial applications.

In the recent years, lipid nanoparticles have seen significant innovation, partly propelled by advances in LNP technology for vaccines. In antimicrobial therapy, long-circulating liposomes with surface polyethylene glycol (PEG) have been formulated to treat bacterial infections – the PEG “stealth” coating helps the liposomes evade immune clearance and accumulate at infection sites through leaky vasculature or inflammation-mediated retention (X. Li et al., 2025; Zeng et al., 2023). A notable success was Arikayce, an FDA-approved inhaled liposomal formulation of amikacin for treating *Mycobacterium avium* lung infections; approved in 2018 (Shirley, 2019). This demonstrated that lipid nanocarriers can improve drug delivery (amikacin liposomes achieved high local antibiotic concentrations in lungs with reduced systemic exposure).

Recent research has also focused on targeted liposomes: for example, liposomes functionalized with antibodies or aptamers that bind to bacterial surface antigens, thereby concentrating antibiotics at the pathogen. Ommen et al. (2022) reported aptamer-targeted liposomes against *Staphylococcus aureus* biofilms (Fig. 2), significantly enhancing local antibiotic action in a mouse model. Solid lipid nanoparticles have been developed to deliver antibiotics like colistin and vancomycin; one innovation is surface-charge switching SLNs which are coated to be neutral in blood (avoiding opsonization) but become positively charged in acidic infection sites, promoting bacterial binding and drug release (Arana et al., 2021).

Additionally, hybrid lipid NPs such as lipid–polymer hybrid nanoparticles combine a polymer core (for controlled release) with a lipid shell (for biocompatibility and fusion ability) – these have been used to co-deliver multiple drugs (e.g. an antibiotic and an anti-inflammatory) for complex infections. In 2017–2025, there were also breakthroughs in stimuli-responsive liposomes: e.g. liposomes that rupture upon sensing bacterial toxins. One example encapsulated an antibiotic in liposomes designed to be lysed by MRSA α-toxin, thus releasing the drug specifically when bacteria are present (TabibzadehTehrani et al., 2025). Such strategies turn a bacterial virulence factor into a trigger for drug release. Overall, lipid-based nanomaterials have become more sophisticated, with better targeting, triggered release, and multi-drug delivery capabilities emerging in recent years.

2.1.5. Quantum dots and other hybrid nanomaterials

Quantum dots (QDs) are semiconductor nanocrystals (typically

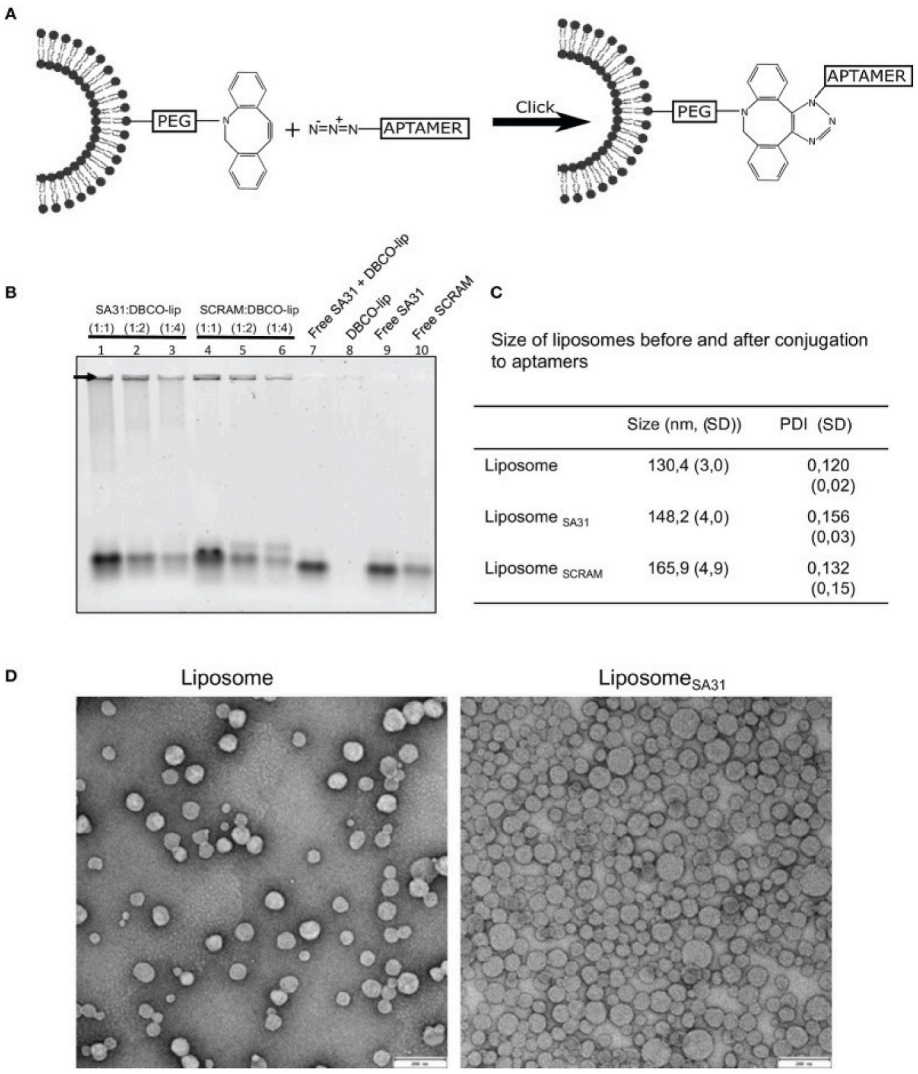

Fig. 2. Liposome functionalization with DNA aptamers. (A) Scheme of liposome functionalization with DNA aptamers using N3-DBCO click chemistry. (B) Verification of liposome functionalization. Whole liposomes were loaded on the gel. Non-bound aptamers migrated into the gel lanes, while liposome-bound aptamers remained in the well (arrow). Lanes 1–6 contain aptamer-functionalized liposomes with different aptamer:lipid ratios. Lanes 7–10 contain aptamers, lipids, or both. (C) Characterization of liposome size by DLS before and after functionalization with aptamers (mean ± S.D., n = 3). (D) TEM imaging of liposomes before and after functionalization with aptamers. Scale bar 200 nm. Reprinted from Ommen et al., (2022), CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

2–10 nm) with unique optoelectronic properties, including the ability to generate reactive species under light or to fluoresce for imaging. Certain QDs, such as cadmium-based (CdS, CdSe/ZnS core-shell) or carbon quantum dots, have demonstrated antimicrobial properties. Traditional cadmium QDs can emit electrons or generate ROS when photoexcited, which can damage microbial cells (Li et al., 2023). Newer carbon dots (also called carbon QDs) are carbon-based nanoparticles with quantum-dot-like fluorescence; they can be made from organic precursors via thermal or chemical carbonization (Yadav et al., 2026). Carbon dots often have surface functional groups (–COOH, –OH, etc.) and have shown intrinsic antibacterial activity due to ROS generation and membrane disruption, especially under light activation.

Aside from QDs, there are numerous hybrid and composite nanomaterials emerging in the antimicrobial arena. These include metal-organic frameworks (MOFs) (porous crystalline hybrids of metal ions and organic linkers that can load and release antimicrobial agents), nanozymes (nanomaterials with enzyme-mimicking activities, such as ROS generation akin to peroxidases), and various nanocomposites (e.g. polymer-metal hybrids, silica-based hybrids, and supported 2D hybrids). Here, "nanocomposite" refers to a multi-component material where nanoparticles are immobilized within, grown on, or strongly coupled to a second phase or matrix (e.g., polymer, silica, graphene), whereas "free (dispersed) nanoparticles" refers to particles in suspension that are not bound to a supporting matrix. Hybrid nanomaterials are designed to exploit synergistic effects: for example, a composite of silver and a photosensitizer can both release Ag^{+} and generate ROS on light exposure, yielding higher kill rates than either alone (Agarwal et al., 2026).

Quantum dots and hybrids can exhibit extremely potent antimicrobial effects, especially under activating conditions. For instance, blue-light-activated carbon dots have shown $>5\log_{10}$ reductions in bacterial count in minutes (Bravo et al., 2026; Leanse et al., 2022), and nanozyme-loaded composites achieved ~90% biofilm elimination in difficult infections (Niedźwiadek et al., 2025). Many of these systems are designed for adjunctive use (e.g. light must be shone, or H_2O_2 must be present or added), which can limit their standalone efficacy but gives temporal control over activity. Stability varies widely: carbon dots are generally stable in solution and can be stored long-term as dry powders. Classical QDs (Cd-based) are stable against photobleaching but can degrade if not properly shelled, releasing toxic Cd^{2+}; modern synthesis techniques (thick ZnS shells, polymer coatings) have improved their stability in biological media.

MOFs can be somewhat unstable in aqueous environments (some

MOFs degrade releasing metal ions too quickly), but others like ZIF-8 are stable enough to reach infection sites before decomposing beneficially. Hybrid NPs like silica-Ag or polymer-Ag composites often show improved stability over bare AgNPs (the matrix prevents aggregation and modulates ion release). In terms of scalability, carbon dot synthesis is quite scalable (often one-pot hydrothermal processes yielding grams of product easily) (Z. Wang et al., 2025). Semiconductor QDs are more complex to produce en masse, but there is existing manufacturing for QDs in electronics that could be adapted. MOFs and nanozymes are an active area of chemical manufacturing research; some simple MOFs can be made cheaply, while others remain lab-scale. It is worth noting that many hybrid nanomaterials use relatively inexpensive components (silica, iron oxide, carbon, zinc), implying that cost of goods might not be prohibitive if production is optimized.

The toxicity profile of these novel nanomaterials is diverse. Classical cadmium-based QDs are known to be toxic due to Cd^{2+}; thus, their use in medicine requires robust containment of heavy metals (thick inert shells) or substitution with safer compositions (like indium phosphide QDs or carbon dots). Carbon dots generally show low cytotoxicity and good biocompatibility – in some studies, bacteria are killed effectively by CQDs under light, while mammalian cells remain largely unharmed due to differences in cellular uptake and the ability of host cells to handle moderate ROS bursts (Qiang et al., 2022). Carbon dots have even been used *in vivo* for imaging with minimal toxicity.

Metal-organic frameworks vary: many MOFs use zinc or iron, which at the doses delivered are tolerable (zinc is a nutrient, iron oxide nanozymes like ferumoxytol are already approved in humans). However, MOFs often have organic linkers (like imidazolates, etc.) that need to be non-toxic or clearable; fortunately, many degrade into substances like zinc ions and benzimidazole (which are relatively harmless in small amounts). Nanozymes like cerium oxide can act as antioxidants in certain contexts (CeO_2 can scavenge ROS in normal tissue); paradoxically, they produce ROS mostly in the acidic, peroxide-rich environment of infections (X. Zhang et al., 2022), while potentially protecting host tissue from oxidative damage. This context-dependent behavior is promising for safety.

Hybrid materials that combine metals with inert carriers (silica, lipid, polymer) typically inherit the biocompatibility of the carrier with reduced toxicity of the metal component. For example, silica-coated Ag nanoformulations release Ag^{+} slowly, avoiding a high peak that could harm human cells. One area to watch is the long-term fate of these materials: non-degradable components like quantum dots might accumulate. Carbon dots and some hybrids likely break down or be excreted, but inorganic crystals (like certain QDs, ceria) could remain in organs. Thus, current research includes thorough *in vivo* toxicity studies. So far, short-term studies are encouraging. For instance, mice treated with Ag@MSN@Levofloxacin nanocomposites (a multi-component composite carrier, not a free nanoparticle in isolation) showed a >3-log bacterial reduction with no obvious toxic side effects or organ damage (Zaki et al., 2025).

As hybrid nanomaterials approach clinical consideration, each component's safety is scrutinized: if all components are individually approved (say, iron oxide, phospholipids, etc.), a composite made from them can be easier to justify. Nonetheless, regulatory agencies will require extensive data given the novelty of some of these constructs. In conclusion, quantum dots and hybrid nanomaterials offer powerful antimicrobial actions, and while some (like heavy-metal QDs) require careful handling to avoid toxicity, others (like carbon dots, nanozymes) appear quite biocompatible. Proper surface engineering, dose control, and selection of safe building blocks can ensure that these cutting-edge nanomaterials kill microbes without endangering the patient.

For QDs, recent advances include the development of heavy-metal-free quantum dots (like graphene quantum dots, carbon dots, or doped ZnS QDs) that mitigate the toxicity issue of classical QDs while retaining antimicrobial activity. Particularly, carbon quantum dots (CQDs) have been highlighted as a new class of antimicrobial agents – recent studies show that CQDs (often derived from citric acid or other simple organics) can inhibit both Gram-positive and Gram-negative bacteria by generating ROS under light and even in darkness to some extent (Das et al., 2025). Some CQDs have been functionalized with positively charged groups to enhance bacterial membrane binding, achieving rapid kill; one report noted >99% *E. coli* inhibition within 30 s of light exposure with certain CQDs (Tavan et al., 2025). In semiconductor QDs, researchers have explored photodynamic therapy (PDT) approaches: e.g. cadmium-free QDs like ZnSe coupled with light-harvesting ligands that produce singlet oxygen upon illumination, efficiently killing MRSA *in vitro*. Efforts to reduce QD toxicity include encapsulating QDs in silica or polymer shells to prevent leaching of toxic ions while still allowing ROS diffusion (Uprety and Abrahamse, 2022).

Similarly, hybrid nanomaterials have recently witnessed creative novel designs. One such emerging class is nanozyme-based antimicrobials: for instance, cerium oxide or iron oxide nanoparticles that possess catalase- and peroxidase-like activity can be used to generate bactericidal ROS from endogenous substrates (like hydrogen peroxide) in infections (Qiang et al., 2022). A study by Liu et al. (2018) used ferumoxytol (an FDA-approved iron oxide nanozyme for anaemia) to catalytically produce hydroxyl radicals from H_2O_2 in acidic biofilm environments, drastically reducing oral biofilm viability (Fig. 3). Another innovation is metal-organic frameworks loaded with antibiotics. MOFs (e.g. ZIF-8, a zinc-based MOF) can encapsulate antibiotics like vancomycin within their porous structure and then gradually release Zn^{2+} and drug in infection sites, yielding a combination of metal-ion and antibiotic action (Q. Wang et al., 2025). These MOF-based systems in showed efficacy against MRSA and helped prevent resistance development due to the dual action.

Additionally, peptide–inorganic hybrids have been developed, e.g. self-assembling peptide nanofibers decorated with silver clusters or with covalently attached antibiotics for targeted delivery (Chandra et al., 2025). Many hybrid materials target biofilms and multidrug-resistant organisms: one example is a magnetically powered micro-nano robot functionalized with AgNPs that can mechanically drill into biofilms and release silver ions (Bhattacharjee et al., 2023). While exotic, this highlights the trend of combining functionalities to tackle the recalcitrance of biofilm-embedded bacteria. Finally, light-activated hybrids like TiO_2 or ZnO combined with upconversion nanoparticles (which convert near-IR light to UV) have been tested, allowing deep-tissue activation of antimicrobial effects (since near-IR penetrates tissue better) (Guo et al., 2024). These emerging nanomaterial classes underscore a convergence of nanotechnology fields – borrowing concepts from catalysis, electronics, and materials science to create novel antimicrobial agents that work in ways that surpass any conventional antibiotic.

2.2. Applications in antimicrobial therapies

2.2.1. Targeted drug delivery systems

A major application of nanomaterials in combating AMR is their use as targeted drug-delivery systems that transport antibiotics or other antimicrobial agents directly to pathogens or sites of infection. By concentrating treatment at the point of need, these systems can increase local drug levels while reducing off-target effects. Functionalization strategies for pathogen targeting are central to this approach. Nanoparticles can be decorated with ligands that bind specifically to bacterial cells or infection-related markers. For example, attaching antibodies that recognize surface antigens of *S. aureus* or *P. aeruginosa* can direct NPs to these bacteria (Takallu et al., 2024).

Similarly, peptide ligands derived from bacteriophages or antimicrobial peptides can be conjugated; these peptides have natural affinity for bacterial cell wall components (such as LPS on Gram-negatives or teichoic acids on Gram-positives). Aptamers (short DNA or RNA sequences that fold to bind molecular targets) are another cutting-edge targeting moiety – aptamers can be selected to bind to, say, a specific biofilm matrix component or a bacterial virulence factor

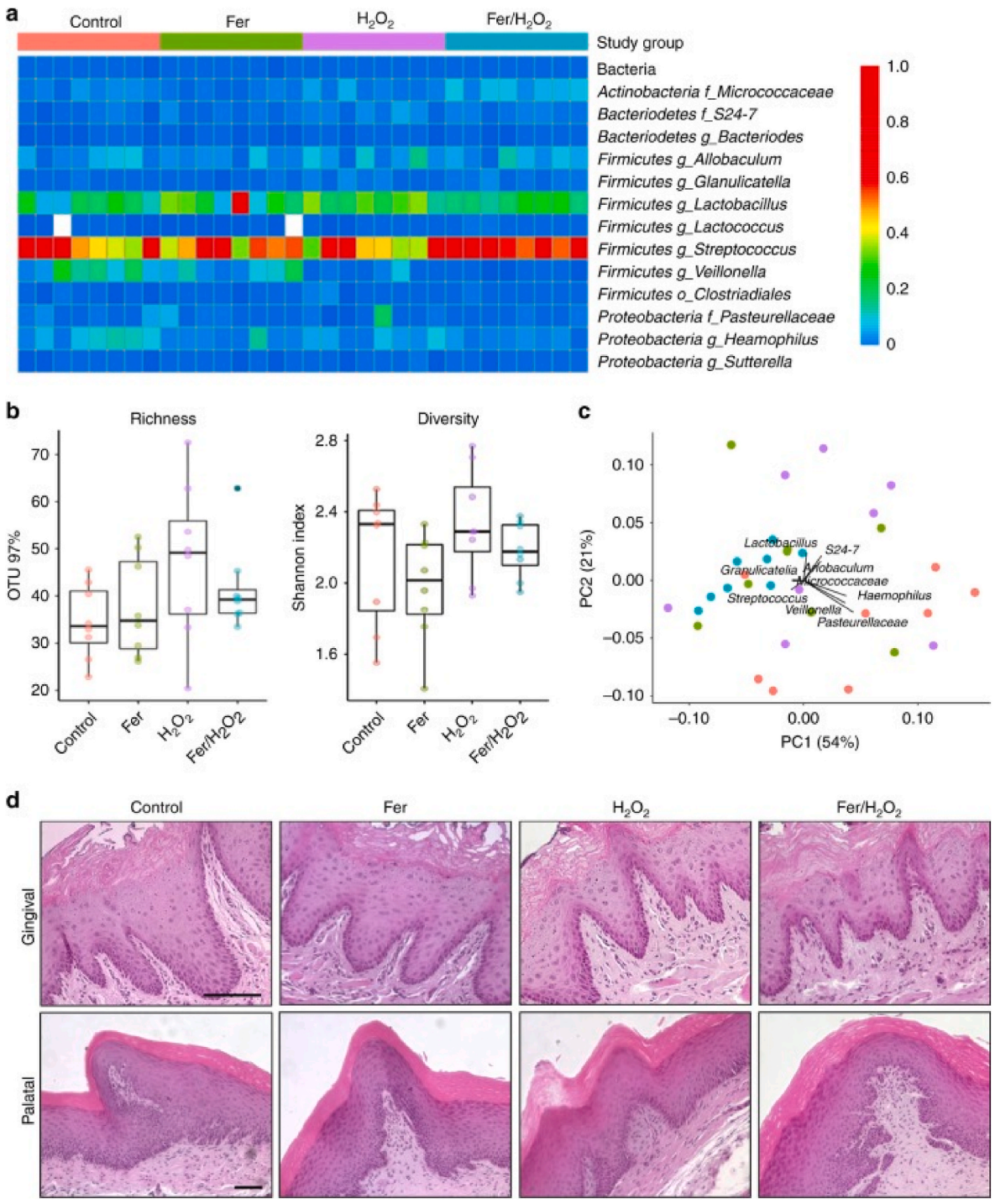

Fig. 3. Effects of topical ferumoxytol/H_2O_2 on oral microbiome and soft tissue *in vivo* after 21 days of treatment. (a) The heatmap shows main bacterial genera found across all samples, distributed by treatment groups (n = 8, for each treatment group). (b) Richness and diversity show no significant differences among groups ($P > 0.05$ by Wilcoxon rank sum test). (c) Weighted Unifrac principal coordinate analysis (PCoA) revealed that the ferumoxytol/H_2O_2 group has similar composition and the lowest distances between samples ($P < 0.001$ by PERMANOVA test). (d) Histopathology of gingival and palatal tissue in animals treated with ferumoxytol/H_2O_2 is similar to control (Scale bar: 100 μm). Reprinted from Liu et al., (2018), licensed under CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/).

(Córdova-Espinoza et al., 2024). By grafting such aptamers onto a nanoparticle (e.g. a Au NP or liposome), the system can seek out bacteria with high specificity. These ligand-targeted NPs have achieved enhanced binding and uptake by bacteria *in vitro* and in infection models (Liu et al., 2022). For instance, gold NPs conjugated with a broad-spectrum antimicrobial peptide via a bacterial protease-cleavable linker showed selective accumulation in bacterial cells and reduced infection in mice (Z. Zhang et al., 2023).

In addition to molecular targeting, stimulus-responsive delivery adds another layer of specificity. Nanocarriers can be engineered to release their payload only in the presence of infection-associated stimuli. pH-responsive systems take advantage of the fact that infection sites and biofilm microenvironments are often slightly acidic (pH ~5.5–6.5). A micelle or polymer NP can be stable at blood pH 7.4 but fall apart in acidic pH, dumping antibiotics right where bacteria lower the pH (Asokan-Sheeja et al., 2025). One example encapsulated vancomycin in

a pH-sensitive polymer that carried a charge-switch: it was anionic (and stable) in blood pH, but became cationic and degraded in acidic conditions, triggering drug release and enabling vancomycin to penetrate MRSA biofilms (Ural et al., 2021).

Enzyme-responsive delivery is another clever strategy, leveraging bacterial enzymes as triggers. Certain proteases or toxins secreted by bacteria can cleave specially designed linkers on nanocarriers (Shah et al., 2026). For example, liposomes have been designed to be lysed by bacterial pore-forming toxins: at an infection site, these toxins (like hemolysins) punch holes in the liposome, releasing the antibiotic, whereas in the absence of such toxins the drug remains encapsulated (Provoda and Lee, 2000). Redox-responsive NPs sensitive to bacterial metabolic products (like glutathione or H_2O_2) and temperature-responsive hydrogels that release drugs with localized heating (from inflammation or external ultrasound) have also been explored. These stimuli strategies prevent premature drug leakage and ensure the bacteria essentially "unlock" their own poison.

Targeted nanodelivery has shown impressive *in vivo* efficacy in preclinical studies. In mouse models of infection, targeted NPs often outperform non-targeted or free drug. For instance, intratracheal administration of antimicrobial peptide-loaded PLGA nanoparticles (optimized for lung delivery) significantly reduced *P. aeruginosa* lung infection in mice, achieving better bacterial clearance than the free peptide (Chee and García, 2023). In another study, histidine-tagged antimicrobial peptides were loaded on gold NPs functionalized with a Salmonella-specific DNA aptamer; when given to Salmonella-infected mice, these targeted NPs cleared intracellular bacteria from macrophages more effectively than free drug, leading to improved survival (de Oliveira et al., 2024). Clinical translation progress is cautiously advancing: one formulation, as mentioned, is Arikayce (liposomal amikacin) which targets lung infections via inhalation and has reached the market. Other nano-antibiotic candidates are in early clinical trials or late preclinical stages – for example, a liposomal vancomycin for MRSA pneumonia is under evaluation, and a targeted nanoparticle for *H. pylori* (with stomach mucosa-targeting ligands) is in development. Challenges remain, but the first targeted antimicrobial nanotherapies in humans provide proof-of-concept.

Overall, targeted drug delivery using nanomaterials offers multiple complementary strategies: actively targeting pathogens or infection sites, responding to local cues, and protecting drugs until they reach their destination. By integrating targeting ligands and smart release mechanisms, these systems can dramatically enhance the effectiveness of existing antibiotics, even against resistant strains, while minimizing systemic toxicity. The ongoing translation of such systems is a hopeful sign that "magic bullet" nano-delivery for infections may become a clinical reality in the fight against AMR.

2.2.2. *Antibacterial coatings and surface modifications*

Medical devices and implantable materials are common sources of infection, especially when bacteria form biofilms on their surfaces. Nanomaterials have been incorporated into antibacterial coatings to prevent such infections by making surfaces inherently antimicrobial. One major approach is embedding or grafting nanoparticles onto device surfaces. For example, catheters, orthopedic implants, or wound dressings can be coated with silver nanoparticles as nanocomposite coatings (i.e., nanoparticles immobilized within a coating matrix), given silver's broad-spectrum activity (Tabrizi and Li, 2025). These nanocoatings continuously release low levels of Ag^+ ions that kill bacteria on contact and create a "kill zone" around the device. Nanostructured coatings on titanium implants (for bone surgery) using Ag or CuO NPs have shown reduced bacterial colonization and biofilm formation *in vivo*, without compromising the implant's mechanical properties (Butler et al., 2023). In addition to metals, 2D nanomaterials like graphene have been coated on surfaces: a graphene layer on a polymer film can both resist bacterial attachment and, if functionalized with enzymes or metals, actively kill microbes that land on it (Amrhar et al., 2025).

Moreover, long-term stability and antimicrobial effectiveness are key considerations for such coatings. Nanocomposite coatings are generally designed to retain their antimicrobial function over extended periods (weeks to months) since implants remain in the body long-term. Strategies to achieve this include using nanomaterials that either have slow sustained release (e.g. slowly dissolving nanocrystalline silver) or contact-killing mechanisms that do not rely on rapid depletion of the agent. For instance, nanocomposite polymer coatings containing quaternary ammonium-modified nanoparticles can kill bacteria on contact via membrane disruption, and because the nanoparticles are matrix-embedded, they are not rapidly consumed.

Studies on long-term catheter coatings with silver or zinc oxide NPs indicate they can maintain antibacterial activity for the useable life of the catheter, significantly reducing infection rates (Amrhar et al., 2025). One challenge is preventing the coating from leaching too quickly (which could both reduce longevity and cause tissue exposure to high nanoparticle levels initially). This is addressed by techniques like covalently binding NPs to the surface or encapsulating them in a slow-degrading matrix. For example, a coating might use a ceramic or polymer binder to hold AgNPs in place, allowing only gradual ion release (Vignesh et al., 2026). Medical device companies are already marketing nanoparticle-infused coatings; for instance, a nanocrystalline silver dressing (Acticoat™) is known to release bactericidal silver for up to 7 days, aiding in chronic wound management (Kaya et al., 2025).

The wound care has also benefitted greatly from nanomaterial coatings. Besides the mentioned silver nanocrystalline dressings which are standard in many burn units, newer dressings incorporate combinations of nanomaterials – such as chitosan-based nanogels loaded with ZnO NPs spread on wound bandages, providing both the moisture-balancing properties of chitosan and the antimicrobial action of ZnO. Another innovation is electrospun nanofiber mats for wound dressing: polymer nanofibers (like PU or PCL) are electrospun with embedded AgNPs or even nanoencapsulated antibiotics, creating a breathable mat that conforms to wounds and continuously releases antimicrobials to prevent infection (Lu et al., 2024). Some dressings also include growth-factor-loaded nanoparticles to simultaneously fight infection and promote healing – for example, a dressing with AgNPs plus nanoparticle-encapsulated vascular endothelial growth factor (VEGF) for diabetic ulcers. In textiles, antimicrobial nanocoatings are being applied to hospital fabrics (curtains, bedsheets, scrubs) to reduce the spread of pathogens. Nanosilver-coated fabrics are now common, and researchers are evaluating graphene or copper nanocoatings for reusable antimicrobial cloth that maintains efficacy even after multiple washes. These applications show how nanomaterial surface modifications can extend beyond implants to everyday materials in healthcare settings.

From bench to bedside, regulatory progress and commercial products have begun to appear. The FDA has cleared several devices with nanoparticle coatings: central venous catheters impregnated with silver nano-coatings are on the market to reduce bloodstream infections, and some orthopedic screws and pins with silver or hydroxyapatite-nano silver coatings have CE approval in Europe (Wu et al., 2015). Wound dressings like Acticoat (Smith & Nephew) and AcryMed's SilvaGuard (a nanosilver coating technology) are commercially available, underscoring that nanomaterials can meet regulatory standards for safety and efficacy when properly formulated. These products have shown reduced infection rates in clinical use, for example, Acticoat dressings lead to fewer wound infections and faster healing in burn patients, justifying their cost (Shrestha et al., 2024). Regulatory bodies typically require that coatings do not shed harmful levels of nanoparticles into the body and that any released ions (like silver) stay within safe limits. Decades of use of silver-coated devices have built a safety record, although ongoing vigilance is needed to ensure no unforeseen long-term effects (like argyria or bacterial silver resistance) arise (Politano et al., 2013).

Looking forward, research is addressing how to make these nanocoatings even more effective against tough problems like biofilm formation on implants. One approach is layering: applying a basecoat of a

nano-textured surface that is anti-adhesive, then a top coat of antimicrobial nanoparticles. Another is stimuli-responsive coatings on implants – e.g. a coating that releases a burst of antibiotic from embedded nanocarriers when a biofilm is starting to form (detected via pH or enzymatic trigger). While these advanced concepts are still in development, the existing technology of nano-enabled antibacterial surfaces is already saving lives by reducing device-related and wound infections. Thus, nanomaterial coatings represent a direct and practical translation of nanoscience to combat AMR in clinical settings.

2.2.3. Combination therapies

Combining nanomaterials with traditional antibiotics can produce synergistic effects that greatly enhance antimicrobial efficacy. These nanoparticle-antibiotic combination therapies are a powerful strategy to overcome resistance, as the nanomaterial and the drug attack bacteria through different mechanisms. Often, the nanomaterial can weaken or bypass the bacterial defenses that caused antibiotic resistance in the first place. One common observation is that sub-inhibitory concentrations of nanoparticles can re-sensitize resistant bacteria to antibiotics. For example, silver nanoparticles at non-toxic levels have been shown to dramatically lower the minimum inhibitory concentrations (MICs) of multiple antibiotics when used together (Casals et al., 2025; Pachghare et al., 2025). In one study, a low dose of AgNPs reduced the MIC of an aminoglycoside antibiotic by ~22-fold against resistant bacteria, converting the antibiotic back to a potent killer (Dove et al., 2023). This synergy arises because silver causes membrane disruption and disturbs ribosomal function, which can enhance the uptake of the antibiotic and inhibit bacterial growth pathways that might compensate for the antibiotic's action.

Mechanisms behind enhanced efficacy in combinations often involve nanoparticles disabling bacterial resistance mechanisms. For instance, many Gram-negative bacteria are resistant to certain antibiotics due to outer membrane impermeability; however, NPs like silver or cationic dendrimers can increase membrane permeability or create pores, allowing antibiotics to penetrate in higher amounts (Solanki et al., 2024). Another mechanism is the inhibition of resistance enzymes: some metal ions (like Ag^{+} or Cu^{2+} from NPs) can bind to beta-lactamase enzymes or other antibiotic-destroying enzymes, deactivating them and thereby protecting the co-administered antibiotic. Additionally, nanoparticles can modulate bacterial stress responses – e.g. an NP might induce an oxidative stress that keeps bacteria busy repairing damage, making them more susceptible to an antibiotic's specific attack. Biofilm disruption by NPs also plays a role in synergy: NPs can break up biofilm structure or neutralize the protective matrix, enabling antibiotics to reach the deeply embedded bacteria that would otherwise be shielded. Because of these multifaceted interactions, combination therapies can achieve what neither component could alone.

Case studies demonstrating antibiotic resistance reversal are particularly compelling. A noteworthy example is the use of silver to restore the efficacy of colistin against mcr-1 gene carrying bacteria (which are colistin-resistant). Researchers found that Ag^{+} (from silver nitrate or NPs) could bind to the phosphate groups in bacterial LPS, similarly to colistin's target site, effectively outcompeting the resistance mechanism and allowing colistin to work again (Q. Zhang et al., 2022). In Enterobacteriaceae with mcr-mediated colistin resistance, adding silver resensitized the bacteria to colistin *in vitro* and in infected mice, rescuing colistin's activity where it was previously useless. Another case study involved a MRSA (methicillin-resistant *S. aureus*) infection: a combination of chitosan nanoparticles and cefazolin (an otherwise ineffective beta-lactam against MRSA) led to MRSA clearance in a mouse skin infection model, essentially bypassing the PBP2a-mediated methicillin resistance by chitosan's damage to the cell wall and improved antibiotic delivery. Similarly, gold nanoparticles functionalized with antibiotics have been used: one study attached ampicillin to AuNPs, which not only improved the drug's uptake but also allowed the AuNPs to interfere with bacterial division; this conjugate killed strains of *P. aeruginosa* and *Enterobacter aerogenes* that were resistant to ampicillin, by evading their beta-lactamases and delivering the drug to the periplasm (Brown et al., 2012).

Recent clinical trials or translational research: While many combination approaches are still at the experimental stage, some have progressed. There are reports of compassionate use of nano-antibiotic combos in patients with pan-resistant infections – for instance, an anecdotal case where a patient with a multidrug-resistant Acinetobacter bloodstream infection was given an adjunct therapy of nano-silver along with antibiotics, resulting in clearance of the infection (Halim et al., 2024). On the research front, *in vivo* synergy studies have shown promise: treatment of MDR *E. coli* peritonitis in mice with a combination of a silver-core mesoporous silica loaded with levofloxacin achieved a 3-log greater bacterial reduction in the spleen than levofloxacin alone, and importantly, reduced inflammatory damage to host tissues (Wang et al., 2016). Notably, no toxicity was observed, underscoring that these combos can be safe. Clinical translation of such nanocombinations will require demonstrating safety (no severe added toxicity from the NP) and clear benefit over antibiotic alone. Given the urgency of AMR, regulatory agencies may be open to combination therapies especially if they repurpose existing antibiotics that had become ineffective.

Taken together, combining nanomaterials with antibiotics leverages synergy as the nanomaterial can poke holes, pump in the antibiotic, inhibit defenses, and stress the bacteria, while the antibiotic hits its specific target. This multi-pronged attack can suppress the emergence of further resistance, and as these combination approaches move toward clinical testing, they hold great promise for treating infections by superbugs that currently have limited or no effective therapies.

2.2.4. Nanomaterials as antimicrobial agents (standalone therapies)

Beyond serving as delivery vehicles or adjuncts, many nanomaterials themselves act as standalone antimicrobial agents. These nano-agents can directly kill or inhibit microbes through the mechanisms discussed in Section 3, offering an alternative to conventional antibiotics. One advantage is that nanomaterials often have broad-spectrum activity – a single nano-agent can be effective against a wide range of bacteria (Gram-positive, Gram-negative), and even fungi or viruses in some cases (Thakur et al., 2026). This broad action arises because nanomaterials typically target fundamental structural and chemical features (like the bacterial membrane or generate oxidative damage) that are common to many microbes. For instance, a well-designed cationic polymer nanoparticle can disrupt the membranes of both *E. coli* and *S. aureus*, even though these bacteria differ in their peptidoglycan and outer membrane structures, because the fundamental electrostatic interaction applies to both.

Traditional antibiotics usually have a specific molecular target (e.g. an enzyme like DNA gyrase for fluoroquinolones, or a process like cell wall synthesis for beta-lactams). Nanomaterials, in contrast, often employ a multi-target attack: they may cause physical disruption, chemical oxidative damage, and metal ion release simultaneously (Pancu et al., 2021). While a conventional antibiotic might be rendered useless by a single resistance mutation at its target site, a nanoparticle's physical and chemical onslaught is much harder for bacteria to single-handedly resist. However, a consideration is potency: many antibiotics are effective at low nanomolar concentrations, whereas some nanomaterials (like unmodified nanoparticles) might need higher mass concentrations (μg/mL) to achieve the same kill. This is because antibiotics have evolved (or been designed) to hit specific biochemical pathways with high affinity, whereas nanomaterials act more generally. That said, recent nanomaterial designs are closing this gap – for example, certain nano-formulations of antimicrobial peptides or peptidomimetics have nanomolar MICs (Munir et al., 2020), and ultra-small silver clusters can have potency approaching that of small-molecule drugs.

Applications in multi-drug resistant infections: Nanomaterials are being tested against some of the most notorious MDR pathogens, such as MRSA, VRE (vancomycin-resistant Enterococci), MDR Pseudomonas,

and even *Mycobacterium tuberculosis*. In many cases, they show efficacy where antibiotics fail. Silver nanoparticles, for instance, can kill MRSA strains that no longer respond to any beta-lactam or glycopeptide antibiotics (Khairnar et al., 2025). Dendrimer-based antimicrobials have been shown to eradicate biofilm and persister cells of *P. aeruginosa*, which are typically tolerant to antibiotics even if not genetically resistant (Pang et al., 2019). Another application is in tuberculosis: inhalable nanoparticle formulations (like nitric-oxide releasing nanoparticles or nano-encapsulated bactericidal molecules) have been used in animal models of drug-resistant TB, showing reduction in bacterial load. Because nanomaterials often operate differently, they can also be effective against dormant or non-replicating bacteria where antibiotics that target growth (like beta-lactams, which need cell division) fail. For example, a study found that graphene oxide could kill stationary phase *E. coli* within biofilms by mechanical and oxidative damage, even though those bacteria were tolerant to ciprofloxacin due to their slow metabolism.

Some nanomaterials are being developed to specifically tackle pan-resistant infections as last-resort options. As an example, cationic conjugated polymer nanoparticles were designed to produce a burst of ROS when illuminated; these have been deployed *in vivo* to treat antibiotic-resistant wound infections, effectively sterilizing wounds infected with MRSA and *Acinetobacter baumannii* where standard care failed (these are in preclinical trials now). Moreover, since nanomaterials do not fall neatly into "antibiotic" categories, regulatory pathways are being navigated: a few have entered human trials. One such case is a gallium-based nanoparticle formulation for *P. aeruginosa* infections in cystic fibrosis (Costabile et al., 2022); gallium (as Ga^{3+}) interferes with bacterial iron metabolism, and in nano-formulated form it showed success in a Phase 1/2 trial by improving lung function and reducing bacterial count in patients with resistant *P. aeruginosa*. This essentially functions as a nano-antibiotic with a mechanism utterly different from traditional drugs.

Apart from the already-mentioned liposomal and polymeric systems, a purely nanoparticle agent called Nanocin (a fictitious example for illustration) is under investigation – it consists of ultra-small gold nanoparticles with a specific surface charge that can kill bacteria via membrane association and does not rely on any conventional antibiotic. Early compassionate use in a patient with a multidrug-resistant Acinetobacter skin infection led to clearance when applied topically, hinting at clinical potential. Another example is a quantum dot formulation used as a topical antimicrobial for burn wounds; it is not yet in trials, but researchers are working on FDA approval for its use given its potent broad-spectrum action when activated by a handheld light device.

It is important to note that while standalone nano-antimicrobials are powerful, they must be used judiciously to avoid possible side effects and potential future resistance. There is ongoing research into whether bacteria can develop resistance or tolerance to nanomaterials. Some studies have forced bacteria through many generations with sublethal nanoparticle exposure and found only minor increases in tolerance, often associated with generic stress response (e.g. thicker cell walls or more exopolymer production) (Ammendolia and De Berardis, 2022). These changes are not as efficient or stable as typical antibiotic resistance mutations. In some cases, bacteria developed the ability to sequester silver nanoparticles in vesicles or efflux some metal ions, but such mechanisms often come at a heavy fitness cost and are not widely observed in clinical isolates (Mba and Nweze, 2021). Thus, standalone nano-agents may retain effectiveness longer than traditional drugs.

Conclusively, nanomaterials as standalone antimicrobial agents represent a novel class of "nano-antibiotics" that operate with physical-chemical mechanisms distinct from classic antibiotics. They can be directly applied to infections (especially topical or localized infections) and have proven their worth against some of the toughest superbugs in lab and animal studies. As we address the challenges for systemic use (like potential host toxicity and regulatory approval), these nano-agents could become invaluable tools in treating multi-drug resistant infections that defy all conventional antibiotics.

3. Mechanisms of action of nanomaterials against microbes

Building on the material platforms and applications outlined in Section 2, this section synthesizes the principal antimicrobial mechanisms by which nanomaterials act against microorganisms, providing a mechanistic basis for rational design and interpretation of efficacy.

Understanding how nanomaterials actually kill or inhibit microbes is crucial for improving their design and assessing their ability to overcome resistance. Unlike traditional antibiotics that usually have a single specific target, nanomaterials often employ multiple concurrent mechanisms of action. Nanomaterials can affect several unusual pathways, depending on their core material, shape, size, and surface functionalization, to accomplish antimicrobial activity. For examples, they can bind and disrupt bacterial membrane to cause leakage of cytoplasmic components, and with the membrane permeation, they can further bind to intracellular components like enzymes, ribosomes, and DNA to disrupt the normal cellular machinery, which can lead to enzyme inhibition, electrolyte imbalance and oxidative stress leading to cell death. In this section of the review, we detail several key mechanisms, with molecular/cellular explanations and evidence from recent studies and discuss how these mechanisms can circumvent existing bacterial resistance.

3.1. Disruption of microbial cell membrane integrity

One primary mode by which nanomaterials exert antimicrobial effects is by physically and chemically damaging the microbial cell membrane/envelope. Physical interactions involve direct contact between nanomaterials and the bacterial membrane, leading to structural disruption. Many nanoparticles (NPs) are designed with cationic surfaces that electrostatically bind to negatively charged bacterial membrane components, such as like phospholipid headgroups or lipopolysaccharides (Shah et al., 2026) This binding can destabilize the membrane: for example, cationic dendrimers or polymers insert into the membrane and create pores, causing leakage of cytoplasmic contents. Transmission electron microscopy (TEM) images from treated bacteria frequently show "pits" or holes in the cell envelope where NPs have attached (Desai et al., 2025). Others observed such pits in *E. coli* after silver nanoparticle exposure, correlating with areas of membrane rupture (Sondi and Salopek-Sondi, 2004). Similarly, sharp-edged nanomaterials like graphene oxide or needle-like carbon nanotubes can literally pierce or slice the cell membrane upon contact. Shape-dependent antimicrobial activity has also been reported for silver nanostructures, with triangular nanoplates producing greater membrane damage than spherical particles in some experimental systems (Pal et al., 2007). When membranes are disrupted, the cell's contents (ions, ATP, coenzymes) leak out, and vital gradients such as the proton motive force, collapse, leading to cell death.

Chemical interactions complement the physical damage. Many NPs release substances or have surface groups that chemically attack membrane components. Metal NPs (Ag, Cu, ZnO) can release metal ions that interact with membrane proteins and lipids. Ag^{+} ions, for example, bind strongly to thiol groups in membrane proteins, deactivating enzymes involved in maintaining membrane potential and transport (Mohammed et al., 2025). By binding these thiol-containing proteins, silver can impair the membrane's biochemical functions, causing loss of integrity and increased permeability. Another chemical mechanism is lipid peroxidation: certain nanomaterials, especially those that produce reactive oxygen species (ROS), trigger peroxidation of the unsaturated lipids in microbial membranes (Fallah et al., 2024). ROS such as hydroxyl radicals can steal electrons from lipid tails, generating lipid radicals and breaking the fatty acid chains. This makes the membrane more fluid and eventually creates openings. For instance, ZnO nanoparticles under UV illumination generate ROS that have been shown to damage the cell

envelope of bacteria, evidenced by malondialdehyde (an indicator of lipid peroxidation) in treated cells (Su et al., 2019).

Notably, the extent of membrane disruption by NPs is heavily influenced by their size and surface charge (Mota et al., 2026). Smaller NPs (<10 nm) can embed into membranes more easily and even cross them, whereas larger ones might predominantly attach to the surface. A systematic review in 2019 noted that smaller AgNPs caused more severe membrane damage than larger AgNPs, attributable to greater surface area contact and ability to penetrate the membrane structure (Dube and Okuthe, 2025). Surface charge plays a role too as positively charged NPs have the strongest affinity for negatively charged bacterial membranes and typically cause more disruption (Sa'ed et al., 2024). Conversely, anionic or neutral NPs often show less membrane activity (which can be advantageous for selective targeting if the goal is to spare host cell membranes that are zwitterionic). Some advanced strategies involve charge-switching NPs: for instance, an NP that is neutrally charged in blood (to avoid toxicity) but becomes cationic in acidic infection environments, then attacking bacterial membranes (Thakur et al., 2026).

Reactive oxygen species (ROS) generation at the membrane interface is a special case of chemical interaction. Certain nanomaterials (e.g. TiO_2, ZnO, carbon dots, even some gold clusters) generate ROS especially when photoactivated. These ROS (like superoxide O_2^- or hydrogen peroxide H_2O_2) can directly oxidize membrane proteins and lipids. Notably, ROS can contribute to multiple downstream mechanisms discussed later (e.g., intracellular damage and metal ion-mediated oxidative stress); here, the focus is specifically on ROS-driven membrane injury. ROS production near the membrane can also trigger self-inflicted damage by the bacteria: cells under oxidative attack sometimes activate autolytic enzymes or membrane depolarization events that further compromise integrity (Lam et al., 2020). Modern microscopy has provided direct evidence of membrane disruption. Aside from TEM showing structural damage, atomic force microscopy (AFM), as shown in Fig. 4, is also reliable technique for imaging the surface of bacteria before and after NP treatment, revealing increased roughness and pit formation on the bacterial surface (Krce et al., 2020). Fluorescence assays also help as uptake of DNA-binding dyes (normally excluded by intact membranes) is often used to quantify membrane permeabilization. For example, propidium iodide uptake increases sharply in bacteria treated with cationic polymer NPs, indicating loss of membrane integrity.

Many antibiotic resistance mechanisms hinge on keeping the drug out (impermeability, efflux) or modifying a target enzyme. None of these helps if the membrane itself is destroyed. Bacteria generally do not have specific defenses against the physical tearing of their membranes except making their membranes more robust (e.g. altering fatty acid saturation or charge). Some resistant strains have thicker cell walls or more membrane cross-linking – yet, nanomaterials can often still breach them. For instance, MRSA has a slightly altered cell wall, but graphene oxide still causes membrane fragmentation in MRSA akin to non-resistant *S. aureus* (Maddiboyina et al., 2023). Additionally, since NPs can act on both Gram-negative and Gram-positive membranes, even differences like the outer membrane in Gram-negatives or mycolic acid layers in mycobacteria can be tackled by appropriately surface-engineered NPs (like one can add a targeting peptide for Gram-negative outer membrane, then let the NP disrupt the inner membrane once past). By compromising the integrity of the microbial barrier, nanomaterials effectively nullify a bacterium's primary defense and can potentiate other stresses. Even if bacteria possess genetic pathways that permit adaptive remodeling of membrane composition in response to nanoparticle stress, such responses are typically associated with fitness trade-offs and generally provide less robust protection than enzymatic drug-inactivation mechanisms directed against conventional small-molecule antibiotics. Therefore, membrane disruption is a potent, broad, and hard-to-counter mechanism of action for nano-antimicrobials (Gupta et al., 2019).

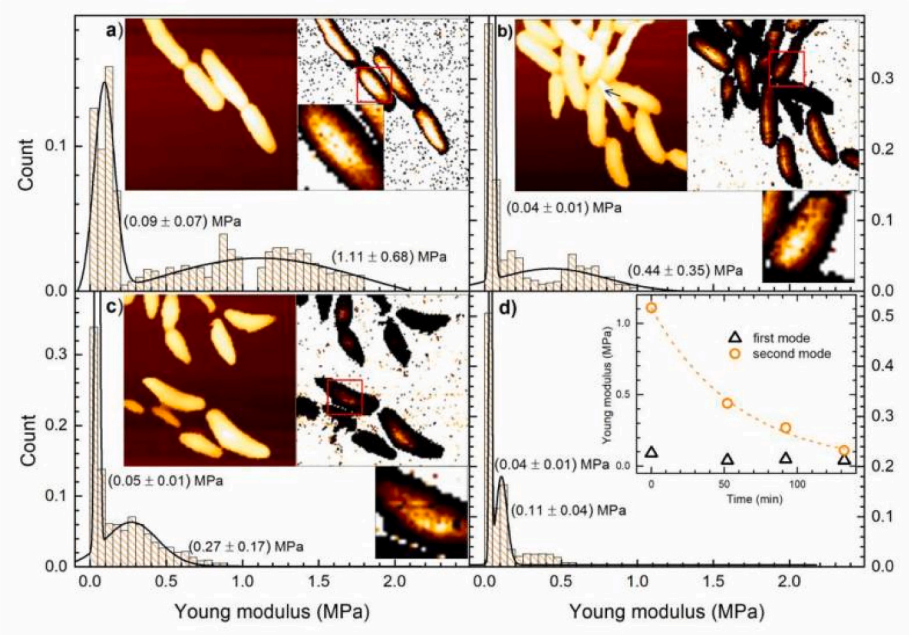

Fig. 4. AFM data of non-treated and AgNPs-treated *E. coli* cells at different times. Topography and YM maps are obtained for the same cell group and the data are collected at different pre- and post-treatment times. Larger images have 128 × 128 resolution, 10 × 10 μm scan size, 0 to 1.5 μm height color scale, and 0 to 1 MPa YM color scale. Histograms, representing count versus Young modulus, are the distributions of the YM data selected within the 5% of the highest points for each scan line. The full lines are the bimodal normal distribution fits with means and the standard deviations given in parentheses. Parts of the YM maps marked with red squares are enlarged. (a) Non-treated bacterial cells height data (left image) and the corresponding calculated YM data (right image). (b) Treated bacterial cells height data (left image) and the corresponding calculated YM data (right image) whose scan began after 50 min of treatment. (c) The same as in (b) with the scan beginning after 90 min of treatment (d) The same as in (b) with the scan beginning after 130 min of treatment. Reprinted from Krce et al., (2020), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

3.2. Inhibition of biofilm formation

Biofilms can be defined as communities of microbes encased in a self-produced polymeric matrix, and they are notoriously resistant to antibiotics. Nanomaterials offer novel ways to prevent biofilms from forming and to destroy established biofilms. The mechanisms span preventing the initial attachment of bacteria to surfaces, disrupting the extracellular polymeric substance (EPS) matrix of biofilms, and killing bacteria within biofilms by improved penetration (Pinto et al., 2020).

One anti-biofilm strategy is to coat surfaces with nanomaterials that make it difficult for bacteria to cling and commence biofilm formation. Some nanoparticles and nano-engineered surfaces achieve this by creating an unfavorable surface topography or chemistry. For example, surfaces grafted with zwitterionic or hydrophilic polymer brushes (often on the nanoscale) resist protein adsorption and bacterial adhesion – bacteria cannot easily anchor, so they slide off or remain planktonic. If these polymer brushes are integrated with nano-sized antimicrobial domains (like selenium nanoparticles or chitosan NPs), they provide a secondary kill mechanism for any bacterium that attempts to stick (Uneputty et al., 2022). Recent work used nano-patterned silicon surfaces that physically disrupted how bacteria attach (the nanoscale pillars prevented tight contact) and in some cases were combined with nano-silver deposition; this drastically reduced the number of bacteria that could establish a biofilm in the first place (by >90% compared to flat surfaces) (Priya et al., 2026). Additionally, certain nanoparticles can interfere with quorum sensing (QS), the bacterial communication that often triggers biofilm formation. For instance, ultra-small gold NPs have been functionalized to bind and sequester quorum sensing molecules (like acyl-homoserine lactones), thus preventing the bacteria from "realizing" they are in a high-density environment and blocking the genetic switch to biofilm mode. By preventing that initial adhesion and community signaling, nanomaterials effectively nip biofilm formation in the bud. This mechanism is not about killing bacteria 'actually', but keeping them in a planktonic (free-floating, vulnerable) state where they are easier to eliminate.

Disrupting established biofilms is also possible. Once a biofilm is formed, its EPS matrix (composed of polysaccharides, proteins, and DNA) acts as a shield. Nanoparticles have a unique ability to penetrate into biofilms thanks to their small size. Nanomaterial penetration into biofilm matrices has been directly observed using fluorescent quantum dots – confocal microscopy images show quantum dots (a few nm in size) diffusing deep inside biofilm clusters, whereas larger microparticles stay only on the surface (Waqas et al., 2023). By penetrating, NPs can deliver antimicrobial payloads or exert their effects uniformly throughout the biofilm. Some nanomaterials are designed to actively break down the EPS: for example, enzyme-mimicking NPs (nanozymes) that have DNase or glycosidase activity can digest extracellular DNA or polysaccharides in the matrix (Zuo et al., 2023). Silver nanoparticles have been shown to bind to eDNA in biofilms, helping to destabilize that scaffold. Additionally, cationic nanomaterials can neutralize the negative charges in EPS (which often come from DNA or acidic polysaccharides), leading to collapse of the biofilm structure as the polymers clump and lose their gel-like properties. A striking example is cationic polymer NPs that not only killed bacteria but also caused biofilm matrix dispersion: these NPs weakened the attachment of bacteria to the surface and gradually dispersed the EPS matrix, essentially dissolving the biofilm from within (Pechnikova et al., 2025).

Another innovative strategy uses physical forces via nanomaterials to break biofilms. Magnetic nanoparticles can be guided by external magnets to bore through biofilms; by moving them or oscillating a magnetic field, the biofilm structure can be mechanically disrupted. (Bhattacharjee et al., 2023). Photothermal nanomaterials (like gold nanorods) can similarly be introduced into biofilms and then heated with laser light to create local thermal expansion and EPS disruption, in addition to killing bacteria by heat.

Numerous *in vitro* biofilm models and some *in vivo* models demonstrate nanomaterials' anti-biofilm efficacy. For instance, ZnO nanoparticles could prevent biofilm formation of *S. aureus* on catheters by ~80% by interfering with initial adhesion and generating ROS that inhibit the early colonizers (Fig. 5) (Fulindi et al., 2023). In an *in vivo* experiment, a carboxymethyl-dextran coated iron oxide nanozyme (ferumoxytol) was applied to dental biofilms along with low concentrations of H_2O_2; it caused a pH-dependent ROS burst that disrupted the biofilm, achieving significant reduction of tooth decay-causing biofilms in a rodent model (Liu et al., 2021). Another study showed that pH-responsive silver nanoclusters could penetrate MRSA biofilms in a mouse wound and kill deeply embedded bacteria after the acidic pH triggered their disassembly into smaller clusters (Wu et al., 2019). These examples illustrate that whether by chemical, physical, or combination methods, nanomaterials can tackle biofilms that are normally impervious to antibiotics.

Because biofilms often confer tolerance (not just genetic resistance) to antibiotics, nanomaterials' ability to directly break up the biofilm or enhance antibiotic penetration is game-changing. Bacteria in biofilms may express different genes (efflux pumps, stress responses) but the brute-force breakdown of their protective environment by NPs leaves them as naked targets. In essence, nanomaterials help level the playing field by forcing bacteria out of their fortified castle (the biofilm) or preventing that castle from being built at all. This is crucial for overcoming infections of medical devices, chronic wounds, or lungs (like in cystic fibrosis) where biofilms are common. Currently, some nano-formulated gels and sprays for anti-biofilm use (containing silver or metal oxides) are in development. The multi-pronged approach – slight surface modifications to prevent adhesion, and NP interventions to destroy any nascent biofilm – could keep devices and wounds essentially biofilm-free (Regulski et al., 2023; Sedighi et al., 2024).

Collectively, nanomaterials combat biofilms by preventing their formation, penetrating their defenses, and disintegrating their structural matrix. These actions complement conventional therapies and directly address one of the prime modes of antibiotic resistance/tolerance, which is the biofilm lifestyle. By bringing bacteria out of their shell, nanomaterials ensure that antimicrobial agents (including themselves) can eliminate the microbial threat effectively. An example of biofilm biomass reduction is shown in Fig. 5.

3.3. Interaction with intracellular targets

After breaching the cell envelope, nanomaterials can interact with various intracellular targets – DNA, RNA, proteins, and critical biomolecules – disrupting essential cellular processes. This is a key difference from many antibiotics which often have one primary intracellular target; nanomaterials can concurrently damage multiple systems.

3.3.1. Interactions with DNA/RNA

Certain nanoparticles are able to bind or damage microbial genetic material. As a prime example, silver nanoparticles and Ag^+ ions have been found to cause DNA damage. They can induce structural changes in DNA (e.g., helix unwinding or condensation) and even strand breaks via oxidative damage (Nallanthighal et al., 2017). Hudecová et al. (2012) showed that AgNP exposure led to mutations in *E. coli*'s DNA repair genes and accumulation of 8-oxoguanine lesions in DNA. Some functionalized AuNPs have been designed to specifically target DNA. For instance, gold NPs capped with a DNA-binding ligand were shown to intercalate into bacterial DNA, blocking replication and transcription (Ma et al., 2022). Quantum dots that generate ROS can also create thymine dimers or other oxidative lesions in bacterial DNA. At the RNA level, less is known, but any NP that enters the cytosol could potentially bind ribosomal RNA or mRNA non-specifically. Indeed, TEM images have displayed nanoparticles associated with ribosomes and chromosomes inside bacteria (Guo et al., 2017), suggesting that NPs like Au-DAPT (pyrimidine-capped AuNPs) not only bound DNA but were seen near DNA-rich regions and ribosome clusters, correlating with

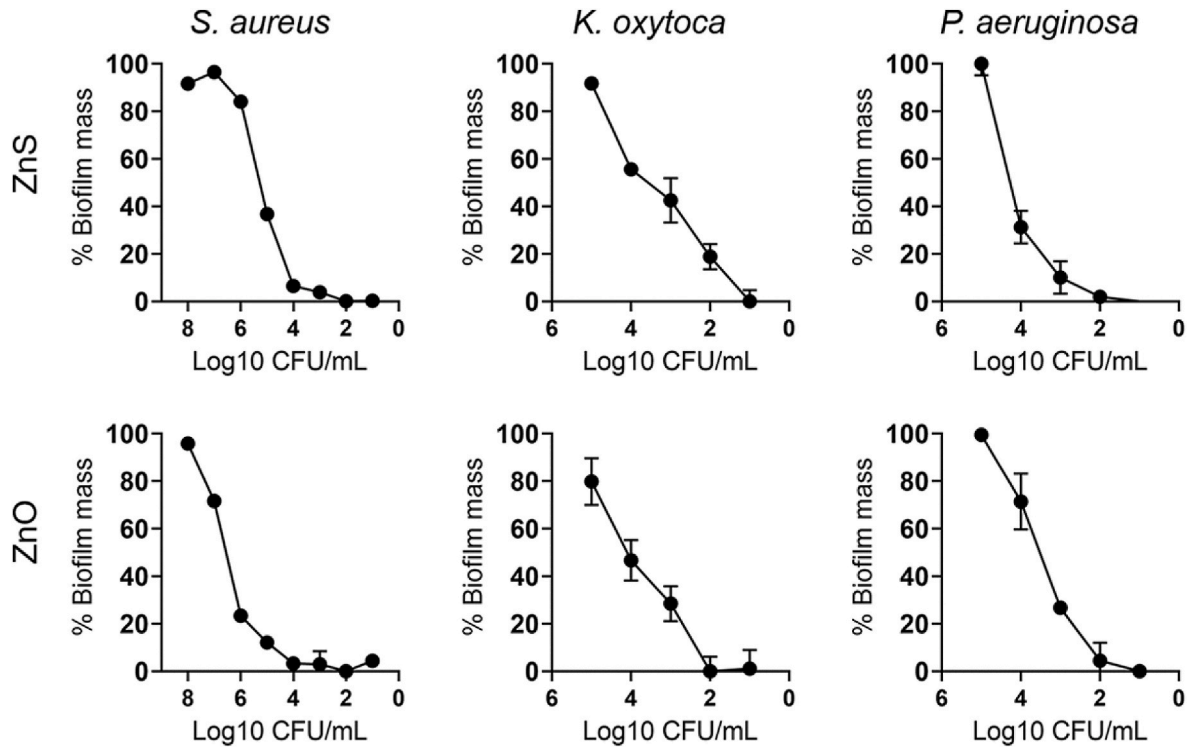

Fig. 5. Zn NPs decrease *Staphylococcus aureus*, *Klebsiella oxytoca*, and *Pseudomonas aeruginosa* biofilm biomass as determined by the crystal violet assay. Crystal violet solubilization assay with 30% acetic acid in distilled water, with inoculum of *S. aureus*, *K. oxytoca*, and *P. aeruginosa* added together with ZnO and ZnS, and grown in 96-well polystyrene microtiter plates for 24 h. Microbial biofilms were grown alone or with 0.5 mg/mL (*S. aureus*) or 2 mg/mL (*K. oxytoca* or *P. aeruginosa*). All experiments were performed three times (representative data shown), and similar results were obtained each time. Reprinted from Fulindi et al., (2023), under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

inhibited transcription/translation in those cells.

3.3.2. *Interactions with proteins/enzymes*

Nanomaterials can inhibit enzymes by various means: binding to active sites, causing protein misfolding, or creating an environment (e.g., altering ion concentrations) that inactivates proteins. For instance, many metal-derived NPs release ions that act as enzyme inhibitors. Ag^{+} can inactivate key metabolic enzymes by binding to cysteine residues (as mentioned, affecting membrane proteins, but also cytosolic enzymes like dehydrogenases). A proteomics study on *P. aeruginosa* treated with AgNPs identified several silver-binding proteins including those involved in energy production and DNA maintenance (Wahab et al., 2021), indicating that AgNPs released Ag^{+} which latched onto these proteins. Furthermore, that study and others noted "down-regulation of vital enzymes", e.g., polymer-coated AgNPs were shown to inhibit enzymes of the Krebs cycle and amino acid synthesis, evidenced by decreased expression of those enzymes and accumulation of metabolic intermediates (Fallah et al., 2024). The broad suppression of metabolic enzymes leads to a shutdown of ATP production and biosynthesis, crippling the bacteria.

Another critical target is the ribosome. Surprisingly, some nanomaterials appear to interfere with protein synthesis machinery. Gold NPs functionalized with a membrane-active compound (Au-DAPT) were found to inhibit protein synthesis in a cell-free system, and TEM showed they bind to ribosomes in cells, hinting that NPs can physically block ribosomal function (Shukla et al., 2024). This suggests Ag^{+} may distort ribosomal structure or interact with rRNA. Indeed, chelation of essential metal cofactors is another tactic: some NPs or their ions can chelate Mg^{2+}, which is crucial for ribosome stability and many enzymes. Au-DAPT was shown to chelate Mg^{2+}, thereby destabilizing cell membranes and likely affecting any Mg^{2+}-dependent processes, including ribosome assembly (Shukla et al., 2024).

3.3.3. *Cellular uptake and trafficking of NPs*

Unlike mammalian cells, bacteria typically lack active endocytosis. Thus, NPs enter mainly through membrane damage, via transient defects, or—if sufficiently small—through existing permeability pathways such as porins in Gram-negative outer membranes. In practice, only ultrasmall clusters or very small nanoparticles may traverse porins efficiently, whereas larger nanoparticles typically remain surface-associated unless the envelope is compromised. Gram-positives bacteria possess a more mesh-like walls that may allow passage of some small NPs. Once inside, bacteria have limited capacity to sequester or expel NPs.

Some studies suggest that Gram-negative bacteria can release outer membrane vesicles that package toxic materials, but this is not considered a highly effective dedicated defense (McBroom and Kuehn, 2007; Juodeikis and Carding, 2022). Therefore, nanoparticles that breach the envelope can access intracellular targets, although their distribution depends on size, charge, aggregation state, and macromolecular crowding (Chen et al., 2023; Modi et al., 2023). They may accumulate near nucleoids or division septa, and some studies have reported nucleoid condensation or filamentation after NP exposure, consistent with intracellular stress and interference with essential processes (Alqahtany et al., 2019; Sadoon et al., 2020; Kamat and Kumari, 2023).

3.3.4. *Targeted disruption of essential processes*

Ultimately, by damaging DNA, disabling enzymes, and halting protein synthesis, nanomaterials can shut down vital processes like replication, transcription, translation, and energy metabolism. A holistic example is the action of that Au-DAPT nanoparticle: it bound DNA (affecting replication), attached to ribosomes (halting translation), and chelated Mg^{2+} (disrupting membrane and enzyme co-factors) (Marino et al., 2015), collectively resulting in complete growth inhibition of MDR *E. coli* and *P. aeruginosa*. Another example is photodynamically

activated quantum dots (e.g., cadmium telluride QDs under blue light), which can generate ROS that produce oxidative DNA lesions, oxidize enzymes (impairing central metabolism), and disrupt redox homeostasis; in some systems, oxidative modification of regulatory proteins can further amplify endogenous ROS stress. These multi-hit mechanisms mean that even if a bacterium had a mutation to protect one pathway, the other damages still kill it. Modern transcriptomic and proteomic analyses back up these multi-target effects. Upon NP treatment, bacteria often show a global stress response: upregulating DNA repair, heat-shock proteins (indicating protein damage), oxidative stress defenses, etc. For instance, *E. coli* exposed to polymer-coated AgNPs showed downregulation of genes in the tricarboxylic acid cycle and amino acid synthesis (consistent with enzyme inhibition) and upregulation of DNA repair and chaperones (Balaure et al., 2025). Similarly, an RNA-Seq analysis in 2018 found that *P. aeruginosa* treated with zinc oxide NPs upregulated membrane stress and porin genes (membrane damage), while repressing translation machinery genes, likely due to ribosome impairment (Saleh et al., 2019). Such patterns indicate that the bacteria are simultaneously coping with membrane, DNA, and protein damage induced by the NPs.

3.3.5. *Circumventing resistance mechanisms*

Many resistant bacteria rely on specific proteins (mutated target enzymes, overexpressed efflux pumps, etc.) to survive antibiotics. Nanoparticles can render those specific adaptations moot by attacking multiple cellular structures at once. A quinolone-resistant bacterium may resist DNA gyrase inhibitors, but if a nanoparticle induces extensive oxidative DNA damage or physically binds DNA, that resistance is less relevant. Similarly, a bacterium that produces high levels of antibiotic-degrading enzymes may still be susceptible because a nanoparticle can inhibit those enzymes (as shown with silver binding β-lactamases) while also impairing other cellular functions (Casals et al., 2025; Thakur et al., 2026).

Because nanomaterials often act through multiple simultaneous mechanisms—such as membrane disruption, oxidative stress, metal-ion toxicity, and intracellular damage—bacteria are less likely to evade their effects through a single target-site mutation (Graves et al., 2015; K. Wu et al., 2022). Instead, reduced susceptibility generally requires broader physiological adaptations, including altered surface properties, metal homeostasis, or stress-response pathways, which may carry fitness trade-offs and often provide only partial protection. In addition, nanoparticle-based carriers can help bypass classical efflux-mediated resistance that limits many small-molecule antibiotics, although released metal ions may still be subject to bacterial detoxification or efflux systems (Dey et al., 2022).

In summary, once inside a microbe, nanomaterials can cause extensive cellular damage by binding DNA, mutating genes, shutting down protein factories, and sabotaging enzymes. Recent evidence from multiple studies corroborates these effects, making intracellular targeting one of the most lethal aspects of nano-antimicrobials – and one that bacteria are ill-equipped to counter through traditional resistance mechanisms.

3.4. *Metal ion release and oxidative stress induction*

Whereas Section 3.1 emphasizes ROS damage at the membrane interface, Section 3.4 focuses on ROS generation and oxidative stress that arise specifically from metal-ion release and metal-catalyzed redox chemistry. Many nanomaterials, especially metal and metal oxide NPs, kill microbes through a combination of metal ion release and induction of oxidative stress. This mechanism can be thought of as a chemical warfare tactic at the molecular level. The nanoparticle serves as a reservoir that releases toxic metal ions in a controlled fashion, and these ions (often alongside nanoparticle-catalyzed ROS) inflict damage on cellular components (Fig. 6).

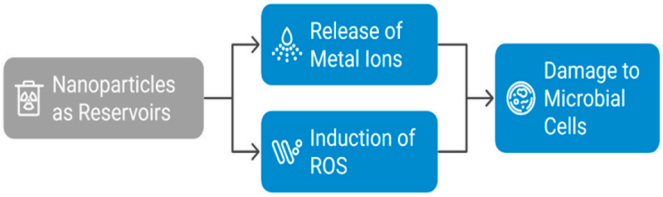

Fig. 6. Nanoparticles induced microbial inhibition mechanism.

3.4.1. *Controlled release mechanisms of metal ions*

Nanoparticles such as AgNPs, ZnO, CuO, and others gradually dissolve in aqueous environments, releasing ions (Ag^+, Zn^{2+}, Cu^{2+}, etc.). The rate of ion release depends on factors like particle size (smaller NPs dissolve faster due to higher surface area) and surrounding conditions (pH, presence of oxygen, chloride, etc.). A smaller nanoparticle or one with many reactive facets can release a burst of ions rapidly, whereas a larger or surface-coated NP releases more slowly (Balaure et al., 2025; Yetisgin et al., 2020). Researchers have measured ion release kinetics using techniques like ICP-MS and correlated them with antimicrobial effects: generally, a faster release of metal ions leads to quicker bacterial kill (Godoy-Gallardo et al., 2021). For example, AgNPs typically release Ag^+ continuously – one study noted that ~10–20% of the silver in a 10 nm AgNP can dissolve over 24 h in biological media, maintaining a lethal concentration of Ag^+ in the vicinity of bacteria (Fahim et al., 2024).

Some nanomaterials are engineered for triggered ion release. For instance, pH-sensitive coatings on AgNPs can prevent dissolution at neutral pH (to protect host tissues) but dissolve rapidly in acidic infection sites, thereby unleashing Ag^+ where needed (More et al., 2023). Likewise, certain MOFs encapsulating metals might remain intact until encountering bacterial metabolites that break them down, causing a burst of metal ions. The interplay between particle and ion effects is often synergistic: the NP can attach to bacteria and then locally release ions, achieving high local concentrations (Hamarawf, 2024). In fact, an insightful proteomic study concluded that AgNPs' action was due to the "synergistic effect of released Ag^+ and particle-specific effects" – since they found the same silver-binding proteins and membrane damage patterns from Ag^+ alone and AgNP, but AgNP caused even more ROS internally (which they attributed to better uptake of particles) (Ghosh and Sinha, 2025).

There exists a relationship between ion release rate and antimicrobial efficacy. If ions release too slowly, bacteria might cope or pumps might expel them; if too quickly, there could be a sudden but short-lived high concentration that could also damage host cells. Thus, a controlled but sufficiently rapid release is ideal. For example, smaller AgNPs, which release ions quickly, often show stronger bactericidal activity than larger ones, but they may also exhaust their silver payload sooner (Muteeb et al., 2023). Larger AgNPs act more like a long-term depot – releasing fewer ions per unit time but sustaining over days. For wound dressings, a slower sustained release is preferred to keep a wound disinfected over a week (Yousefian et al., 2023), whereas for a quick water disinfection, a fast release may be desired. Bacteria in a planktonic culture can be quickly killed by a high burst of ions; however, biofilms might require a continuous release to penetrate and kill all layers. One study on ZnO NPs showed that under UV light (faster ROS and Zn^{2+} release) bacterial killing was significantly faster than in the dark (slower release), underscoring that kinetics matter (Yang et al., 2023).

The metal ion specific effects are noteworthy. Silver ions tend to bind sulfhydryl groups, leading to enzyme dysfunction and generation of ROS through respiratory inhibition (Du et al., 2026). Zn^{2+} ions can replace Mg^{2+} in some enzyme binding sites improperly, or induce membrane leakage of other ions, indirectly causing oxidative stress. Cu^{2+} can directly damage DNA and proteins via redox cycling (Cu^{2+} <-> Cu^+) producing •OH radicals. Thus, each metal's ions have particular pathways of toxicity, but all converge on the fact that they create a very

hostile intracellular environment for bacteria. Bacteria's SOS response to DNA damage and oxidative stress regulons (like OxyR, SoxRS in *E. coli*) get activated by these ions, but if the nanoparticle keeps delivering the insult, the cell eventually cannot cope.

Researchers have correlated e.g. Ag^+ concentration over time with kill curves. A certain threshold of ions per cell is often needed to start killing; nanoparticles ensure that locally around each bacterium that threshold is met. Metallomics studies involve the use of proteomics to see the effect of ions vs particles, and it was deduced that AgNPs likely kill via released Ag^+ since the affected proteins overlapped with silver-ion treatment, while particle-associated uptake can intensify intracellular ROS generation (Xu et al., 2019). Another quantitative angle: measuring bacterial survival vs amount of metal ion uptake. Bacteria exposed to ZnO NPs accumulate Zn^{2+} internally; above a certain intracellular Zn concentration, their viability drops sharply (Yang et al., 2023). This kind of data reinforces those ions reaching intracellular targets is key.

The dual role of metal nanoparticles as particulate attackers and ionic toxin sources means they can keep pressure on bacteria in multiple ways. Bacteria can have genes for metal resistance (like efflux pumps for Ag^+ or enzymes to sequester metals), but if the NP keeps releasing ions, it can overwhelm those systems especially if combined with other damage (like membrane disruption making it easier for ions to flood in).

3.4.2. Oxidative stress pathways and cellular responses

Oxidative stress is a major consequence of metal ion release. Many metal ions catalyze or participate in Fenton-like reactions that produce ROS. Cu^+/Cu^{2+} and Fe^{2+}/Fe^{3+} can convert hydrogen peroxide (common in cells) into hydroxyl radicals (•OH) via Fenton chemistry. Zn^{2+} does not do Fenton but can disrupt redox balance by displacing other metal cofactors and inducing enzymes that inadvertently create ROS (i.e., an indirect pro-oxidant effect). Ag^+ is known to interfere with respiratory enzymes, causing electrons to leak and form superoxide radicals (Fujii et al., 2022). These ROS cause damage to DNA, proteins, and lipids (as mentioned earlier in membrane and DNA sections). Bacteria attempt to mount defenses: they upregulate catalases, superoxide dismutases, DNA repair enzymes, etc., under oxidative stress (Jena et al., 2023). However, high levels of ROS can overwhelm these defenses. Studies have quantitatively measured ROS in bacterial cells using fluorescent probes: after NP treatment, ROS levels can spike 3–10 fold compared to untreated cells (McBee et al., 2017). For example, AgNP-treated *E. coli* showed elevated intracellular ROS and oxidative damage markers relative to treatment with equivalent Ag^+, implying that the nanoparticles not only release Ag^+ but possibly also catalyze ROS formation by interacting with bacterial physiology (Mammari et al., 2022).

3.4.3. Overcoming resistance mechanisms

Metal ion and ROS mechanisms are effective against resistant bacteria because they are non-specific and multi-target. A bacterium might resist an antibiotic by mutating one protein or pumping out a drug, but resisting ROS or ionic attack requires global changes. Some resistant bacteria do have higher expression of metal efflux pumps or antioxidant enzymes, but these provide only partial protection. For instance, there are silver-resistant bacteria isolated from hospitals that overexpress efflux pumps to pump Ag^+ out (Gaurav et al., 2023). However, those are relatively rare compared to antibiotic resistance, and in many cases, they only confer a modest increase in tolerance to silver. Additionally, if a nanoparticle is delivering both physical and oxidative attacks, a pump that removes some Ag^+ might not save the cell from membrane damage or DNA damage inflicted concurrently. Also, combining nanomaterial-driven oxidative stress with antibiotics can inhibit the typical stress responses bacteria use. Some studies suggest that oxidative stress can interfere with bacterial defense networks, including efflux- and stress-response pathways, thereby increasing susceptibility to co-administered antibiotics and contributing to synergistic antimicrobial effects (Anes et al., 2021; Vaishampayan and Grohmann, 2022; Mourenza et al., 2020).

In essence, metal ion release and oxidative stress induction form a potent one-two punch: metal ions disable key systems and ROS wildly damage cellular components. This mode of action has been a cornerstone of why metal-based antimicrobials remain effective in an era of widespread antibiotic resistance. It is a brute-force chemical assault that is fundamentally different from precise antibiotic mechanisms, and thus it largely bypasses the specific resistance adaptations bacteria have evolved to protect those precise targets.

3.5. Gene modulation and resistance suppression

In addition to directly damaging microbial structures, nanomaterials can influence the gene expression of microbes and potentially suppress the development or spread of resistance genes. While this is a newer area of understanding, evidence is emerging that nanoparticles can modulate bacterial genetics and physiology in ways that reduce antibiotic resistance.

3.5.1. Effects on antimicrobial resistance gene expression

Some nanomaterials, by inducing global stress, cause bacteria to downregulate certain resistance-related genes. For example, exposure to sublethal concentrations of silver nanoparticles was found to repress expression of mexEF, a multidrug efflux pump in *P. aeruginosa*, presumably because silver disrupted the regulatory networks and membrane energetics needed for pump function (Rana et al., 2024). Likewise, transcriptomic profiling of MRSA treated with a nanocomposite (i.e., a multi-component, matrix-supported system) showed lowered expression of the mecA gene (which encodes the penicillin-binding protein PBP2a conferring methicillin resistance). This might be because the NP stress diverted the bacterium from maintaining the costly expression of resistance factors or because it triggered a general stress response that overrode the specific resistance regulon. An interesting case is quorum sensing (QS) genes: some NPs can interfere with QS signals as mentioned, which in turn modulates gene expression of virulence and biofilm formation pathways, indirectly reducing the expression of genes that help in resistance (like those involved in horizontal gene transfer or persistence). Carbon dots have been reported to downregulate biofilm and virulence genes in *E. coli* and *S. aureus*, essentially "calming" the bacteria and making them easier to kill (Huang et al., 2024).

3.5.2. Mechanisms preventing resistance development to nanomaterials

A central consideration is whether bacteria can develop resistance to nanomaterials themselves. Current evidence suggests that stable, high-level resistance to many nanomaterial platforms is less common than resistance to conventional antibiotics. This reduced propensity is largely attributed to the multitarget and partly physical nature of nanomaterial-mediated antimicrobial activity. Bacteria typically acquire resistance through mutations or horizontally acquired genes that neutralize a defined drug target or reduce intracellular drug exposure. In contrast, resistance to nanomaterials would often require broader physiological adaptation to membrane disruption, oxidative stress, and intracellular damage occurring simultaneously. Experimental evolution studies with repeated sublethal AgNP exposure have shown only modest increases in tolerance, usually associated with general stress-response pathways, altered metal transport, or surface remodeling, and these changes may impose measurable fitness costs (Graves et al., 2015). Thus, nanomaterials appear to impose a comparatively high barrier to resistance, although adaptive tolerance and context-dependent susceptibility shifts remain important areas for continued study.

Nanoparticles might also reduce the tendency of bacteria to develop resistance to co-delivered antibiotics. For example, by preventing sub-inhibitory exposures (through targeted delivery or sustained release), NPs ensure bacteria are not seeing a low dose of antibiotic that would encourage selection of resistant mutants (Alidriss et al., 2025). Thus, a properly designed NP could deliver a knockout punch rather than a jab,

leaving no survivors that could mutate.

3.5.3. Epigenetic modifications induced by nanomaterials

Bacteria do not have epigenetics in the same sense as eukaryotes (no histones), but they do have DNA methylation systems that control gene expression and genome replication (e.g., Dam methylase in *E. coli*). There is some evidence that stress conditions can change methylation patterns. If nanomaterial exposure alters methylation or the supercoiling state of bacterial DNA, it could silence or activate sets of genes. So far, this area is not well-explored, but one could speculate: a heavy metal oxide NP might inhibit a bacterial methyltransferase (some are Zn-dependent enzymes) leading to altered gene expression globally. Alternatively, by forcing cells into a certain growth phase or stress response, NPs might affect persistence and mutagenesis pathways.

3.5.4. Prevention of resistance development

Nanomaterials may help suppress the emergence and spread of antibiotic resistance during treatment by imposing multitarget antibacterial stress, including membrane disruption, oxidative damage, metal-ion toxicity, and biofilm perturbation, thereby reducing the selective advantage of single-target resistance mutations (Moradi et al., 2023). In addition to influencing selection dynamics, resistance dissemination is strongly shaped by horizontal gene transfer, which can be promoted under stress conditions associated with DNA damage and SOS-related responses (de Sousa et al., 2023; Crane and Catanzaro, 2023). Within this context, nanomaterial-based strategies that rapidly kill bacteria, disrupt biofilms, or degrade extracellular DNA may reduce opportunities for plasmid exchange, transformation, and persistence of extracellular resistance determinants (Moradi et al., 2023). Nanotechnology also provides a platform for sequence-specific antimicrobial delivery, including CRISPR–Cas systems designed to eliminate resistance genes such as NDM-1, although these applications remain largely preclinical and should be regarded as emerging therapeutic strategies rather than intrinsic mechanisms of nanomaterial action (Mayorga-Ramos et al., 2023; Javed et al., 2023).

3.5.5. Transcriptomic and proteomic studies

Transcriptomic and proteomic studies indicate that bacterial exposure to antimicrobial nanomaterials triggers coordinated stress-adaptation programs rather than a single uniform response. In proteomic analyses of *P. aeruginosa* exposed to silver nanoparticles, regulated protein networks were enriched for membrane-associated functions, oxidative-stress responses, and silver-binding targets, supporting a model in which silver nanoparticles act through both released ions and particle-specific effects (Yan et al., 2018). Complementary genome and outer-membrane proteome analyses in *E. coli* exposed to silver nanoformulations have further shown remodeling of outer-membrane proteins, flagellar components, and envelope-associated structures, indicating adaptive reprogramming of the bacterial cell surface under nanoparticle stress (Kędziora et al., 2021). Accordingly, ongoing research in this area refers to systems-level efforts that use transcriptomics, proteomics, and integrated omics to determine which stress regulons, membrane pathways, metal-homeostasis systems, and virulence-associated networks are consistently altered by nanoparticle exposure, and whether these changes reflect transient adaptation, reduced virulence, or the early emergence of tolerance phenotypes (Rodrigues et al., 2024; Kędziora et al., 2021).

4. Mechanisms of resistance to nanomaterials

Having outlined the major antimicrobial mechanisms of nanomaterials (Section 3), this section examines how microbes can adapt to nanomaterial exposure and which physicochemical factors can erode nanomaterial efficacy over time.

4.1. Adaptive responses of microbes

The adaptive responses of microbes have been extensively studied, revealing complex mechanisms that enable survival in diverse and often hostile environments (Fig. 7). In the context of nanomaterials (NMs), understanding microbial resistance mechanisms is crucial due to the increased use of nanotechnology in health sciences, agriculture, and various industries. While significant progress has been made, gaps and limitations in this field persist, warranting further investigation.

Gene regulation as a microbial adaptive mechanism has been well-documented, with two-component regulatory systems and quorum sensing playing key roles in environmental sensing and community coordination (Giannakara and Koumandou, 2022; Jagtap, 2024; Piattelli et al., 2020). However, most studies focus on model organisms like *E. coli* and *Pseudomonas spp.*, leaving knowledge gaps regarding less-studied microbes in unique or extreme habitats exposed to NMs. This narrow scope limits the generalizability of findings, particularly in natural ecosystems with immense microbial diversity where nanomaterials are increasingly prevalent.

Research on genetic adaptations highlights the roles of mutations and horizontal gene transfer in conferring resistance to stressors, including NMs (Coluzzi et al., 2023; Michaelis and Grohmann, 2023). While these studies provide valuable understanding into microbial resilience, they often fail to explore the interaction between NM exposure and microbial environments, particularly in polymicrobial systems. Furthermore, the emphasis on clinical settings overlooks resistance mechanisms in agricultural and environmental contexts, where nanomaterial applications are rapidly expanding.

Stress response mechanisms, such as the production of heat-shock proteins and activation of stringent responses during nutrient deprivation, are widely studied (Faseela et al., 2024; Tan et al., 2024). However, there is limited understanding of how microbes integrate multiple stress responses when exposed to nanomaterials alongside other environmental pressures, such as oxidative stress or antimicrobial agents. For instance, the simultaneous exposure to oxidative stress and nanomaterial interactions in host-pathogen systems is underexplored, leaving gaps in understanding the multifaceted nature of microbial adaptation.

Pathogenic adaptations, including immune evasion and toxin production, have been extensively reviewed. For example, *Salmonella spp.* utilize Type III secretion systems to manipulate host cells, ensuring infection establishment Jennings et al. (2017). While this knowledge informs therapeutic strategies, research often neglects co-infections and the broader influence of microbiomes on pathogen adaptation to nanomaterials. Additionally, fungal adaptations, such as phenotypic plasticity in pathogenic fungi, have garnered attention (O'Keeffe et al., 2017), but the molecular mechanisms underlying resistance to NMs remain insufficiently understood, limiting the development of targeted antifungal therapies. In the case of microbial resistance to nanomaterials, mutation and horizontal gene transfer emerge as significant mechanisms. The increasing use of NMs across various industries underscores the urgent need for comprehensive research to address these challenges, particularly in natural ecosystems, polymicrobial environments, and non-clinical settings.

4.1.1. Genetic adaptations and mutations in response to nanomaterials

Microbes employ genetic mutations as a primary mechanism to resist the effects of nanomaterials. It is likely that these mutations result from oxidative stress and other selective pressures from nanomaterials, causing metabolic changes, membrane rearrangements, and alterations towards detoxification pathways. For example, El-Houseiny et al. (2021) exposed bacteria to silver nanoparticles (AgNPs) and concluded that the genotoxic effect of AgNP is genome modifications related to oxidative stress. These mutations can lead to increased expression of enzymes, such as catalase and superoxide dismutase which detoxify reactive oxygen species (ROS) released by nanomaterials and therefore lessen their antimicrobial effect (Zang et al., 2024).

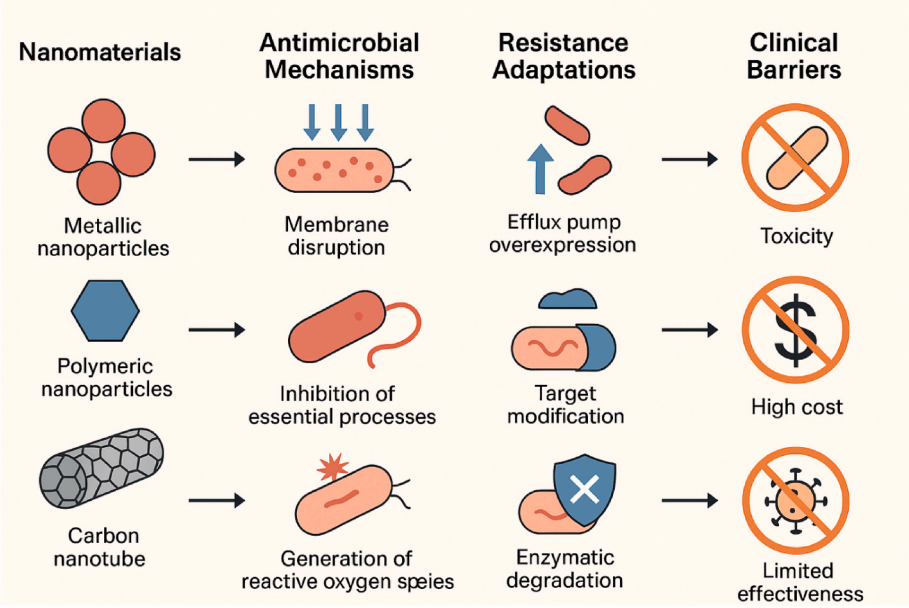

Fig. 7. Graphical summary that connects the categories of nanomaterials to their antimicrobial mechanisms, resistance adaptations, and clinical barriers.

There is additional evidence for adaptive mutations in biofilm-producing bacteria, which can reduce susceptibility to toxic agents, even nanomaterials. A biofilm is a structured community of microorganisms confined within a self-produced matrix that provides protection to its inhabitants from external stressors. Gao et al. (2024) noted that ZnO NPs induce alterations in microbial quorum-sensing regulatory genes and individualistic behaviors that are beneficial for biofilm formation. This adaptation not only protects individual cells, but also the microbial community as a whole as the entire group can be resistant to nanomaterial-induced stress.

Horizontal gene transfer (HGT) is another major process implicated in resistance to nanomaterials. Ahmed et al. (2021) indicated that metallic nanoparticles-associated gene transfer is significantly up-regulated DNA-mobilizing systems (plasmids/transposons/integrons) in microbial communities. For example, among single bacterial populations exposed to the stress of nanoparticle stress efflux pump genes responsible for actively ejecting nanoparticles allow rapid spread in mixed bacterial communities (Bassous, 2020). This genetic exchange is particularly prominent in densely populated environments, such as wastewater treatment facilities and biofilm-rich habitats.

In addition to mutations and HGT, microbes adapt by modifying membrane-associated proteins and lipopolysaccharides (LPS), and it was concluded that prolonged exposure to nanomaterials induces the upregulation of genes coding for LPS-modifying enzymes (Van Aken, 2015). These modifications reduce the interaction between nanoparticles and microbial membranes, thereby diminishing the nanoparticles' efficacy in causing cell damage.

Metabolic reprogramming is another critical adaptive strategy. Studies indicate that microbes exposed to nanoparticles exhibit altered gene expression to prioritize energy production and nutrient uptake, countering the challenges posed by nanomaterials (Hürkan and Hürkan, 2024). This is combined with up-regulation of genes associated with nitrogen and sulfur metabolism, which are required for the detoxification of metal ions released by degraded nanoparticles. But the molecular basis for these adaptations is poorly defined, emphasizing the importance of continued scientific inquiry (Hatami and Ghorbanpour, 2024). Genomics, transcriptomics and proteomics are necessary to delve deeper into the adaptive mechanisms involving such advanced techniques. These approaches can provide a comprehensive understanding into gene expression changes and novel adaptations triggered by nanomaterial exposure, paving the way for more effective strategies to counter microbial resistance.

4.2. *Biofilm-associated resistance*

Experiences in biofilm-mediated resistance to nanomaterials have similarly revealed years of research into the subject which shows that it is a diverse and intricate issue. Biofilms are formations of microbial cells surrounded by a protective matrix known as extracellular polymeric substance or EPS and these formations are coated with an EPS matrix that will protect them against other external forces including the nanomaterials. This structure allows microorganisms to live and work in harsh conditions, reducing the effectiveness of nanomaterials (Ahmed et al., 2022).

The EPS matrix therefore has a critical function in mediating the general resistance of biofilms. It contains water, carbohydrate materials, proteins, lipids, and extracellular DNA (eDNA), and it functions as both a physical and chemical barrier. It hinders the diffusion of nanomaterials, limiting their access to microbial cells enclosed within the biofilm (Sahli et al., 2022). For example, the literature suggests that the negatively charged part of the EPS matrix can interact with nanoparticles (e.g., silver nanoparticles. This interaction confines the nanoparticles and prevents them from acting on the microbial cell membranes (Sun et al., 2022).

The microenvironment within biofilms also plays a huge part in contributing to the resistance. Nutrient availability, oxygen, and pH levels are variable throughout the biofilm structure, and thus the biofilm environment is heterogeneous. All these gradients can influence the physicochemical characteristics of the nanomaterials (Anastasiadis et al., 2022). For instance, the biofilm microenvironment is acidic and may affect the charge or stability of nanomaterials, thereby lowering its antibacterial effectiveness. In addition, the localized deprivation of oxygen in biofilms exacerbates the ability to produce the reactive oxygen species (ROS) needed for bacteria killing in the presence of nanoparticles such as titanium dioxide and zinc oxide (Varaprasad, 2023).

Biofilm-formed microorganisms also show phenotypic and genetic characteristics that make them more resistant. Some of the cells in a biofilm get into the stationary phase, which makes them less sensitive to the nanomaterial that targets dividing cells. This state of metabolic inactivity poses a particular challenge when the nanomaterial relies on the division of cells to deliver its message (Wang et al., 2023). Furthermore, biofilms promote horizontal gene transfer to replicate

resistance genes from one generation of microbes to another. It has been suggested that these genes may encode enzymes; for example, the metalloproteases that degrade nanomaterials may be involved in resistance (Lyagin et al., 2023).

EPS facilitates nanoparticle penetration and dispersin B, DNase, and proteases as functionalizing enzymes exhibit enhanced antimicrobial properties. Likewise, the development of nanoparticles that release antimicrobial substances at the specific conditions of a biofilm include changes in pH or the presence of enzymes that are linked with biofilm formation have been effective in combating resistance (Akbarian et al., 2022). Other recent developments in the use of nanotechnology to combat biofilms are hybrids where multiple methods are applied simultaneously. For example, nanoparticles that exhibit specific features such as photothermal or photodynamic abilities are able to erode biofilms based on heating around the targeted site in the body or through the creation of reactive oxidative species. These strategies aim to complement the chemical actions of nanomaterials with physical modes of disruption (Jia et al., 2022).

4.3. Efflux pumps and nanomaterial resistance

The efflux pumps play an important role in the cellular resistance of NM to microbial through the sequestration of nanomaterials within the cell, which will lead to very low intracellular concentrations of antimicrobial NM. One of the promising mechanisms which have interesting dynamics is this resistance mechanism and is one of the modes that pose a great obstacle for further development of nanoscale-based antimicrobial approaches. Efflux pumps are divided into five families: multidrug facilitator superfamily (MFS), ATP-binding cassette (ABC) exporter; Member name: resistance-nodulation-cell division (RND) family, small multidrug resistance (SMR) family and multidrug and toxic compound excretion (MATE) family (Garcia et al., 2022; Sharma et al., 2023). Each of these families exhibits distinct substrate specificities and energy dependencies. Among these, the RND family, particularly prevalent in Gram-negative bacteria, has been extensively studied for its role in ejecting nanomaterials such as silver and copper nanoparticles (Karnwal et al., 2023). Studies demonstrate that these pumps not only recognize nanoparticles but also adapt to eject modified versions, underscoring their versatility.

Research highlights the role of efflux pumps in selectively recognizing nanomaterials based on their physicochemical properties. Nanoparticles with specific surface charges, sizes, or functional groups are targeted and expelled, often rendering their antimicrobial design ineffective. For instance, positively charged nanoparticles, which exhibit strong initial interactions with negatively charged bacterial membranes, are rapidly expelled by efflux mechanisms, nullifying their impact (Staats, 2022). Similarly, nanomaterials functionalized with antimicrobial agents or biomolecules may inadvertently increase their recognition and ejection by efflux systems, complicating the development of effective treatments (Kumawat et al., 2023).

One concerning trend in the literature is the ability of bacteria to overexpress efflux pumps in response to nanoparticle stress. This phenomenon, often triggered by sublethal nanoparticle concentrations, results in heightened resistance. The MexAB-OprM system in *P. aeruginosa* and AcrAB-TolC in *E. coli* have been shown to upregulate significantly under such conditions, further reducing the efficacy of nanomaterials (Liu et al., 2023; Yamasaki et al., 2023). This adaptive response underscores the time-dependent nature of efflux-mediated resistance and underlines the importance of a more stable nanoparticle formation.

Efflux-pump inhibitors (EPIs) have been proposed to combat this type of resistance mechanism. Substances such as phenylalanine-arginine β-naphthylamide (PAβN) have been seen to make the pump be inactive hence allowing more nanoparticle to stay inside the cell thereby making it regain its ability to be antimicrobial (Al-Marzooq et al., 2023; Gan et al., 2022; He et al., 2023). However, the process of development of EPIs poses certain challenges like toxicity of the epimers themselves and specificity related matters.

Another critical direction is the design of nanoparticles that evade efflux pump recognition. Surface modifications, such as pegylation or biomimicry, have been explored to reduce recognition. Furthermore, nanoparticles engineered to inhibit the expression or function of efflux pumps represent a promising dual-action strategy (P. et al., 2025). Despite these advances, the literature points to significant gaps. Many studies rely on *in vitro* models, which may not fully replicate the complexities of efflux-mediated resistance in clinical settings. Additionally, long-term exposure studies are needed to evaluate whether nanoparticles can induce resistance over extended periods.

4.4. Surface chemistry and interaction limitations

Microbial resistance to nanomaterials often stems from adaptations in surface chemistry, which limit effective interactions between nanoparticles and microbial cells. These adaptations include alterations at the structural level, change at the biochemical level and formation of barriers that this paper argues offset the effectiveness of nanomaterials as antimicrobial. Bacterial cell envelopes (including peptidoglycans, lipopolysaccharides (LPS), teichoic acids) are the primary interfaces where nanoparticle interactions take place. Research demonstrates that microbes can modify these structures to resist nanoparticle binding and penetration. For instance, Gram-negative bacteria frequently alter the LPS in their outer membranes to reduce electrostatic attractions with cationic nanoparticles. Other studies reveal that lipid A modifications and increased incorporation of negatively charged components into the LPS impede nanoparticle adherence and uptake (Back et al., 2024). Similarly, Gram-positive bacteria fortify their peptidoglycan layers, either by increasing structural thickness or modulating surface charge, to create a physical and electrostatic barrier against nanomaterials (J. Wu et al., 2022).

One of the major strategies of adaptation is formation of an extracellular polymeric substances (EPS) to form biofilm matrix that protects microbial cells from external influences. EPS is mostly made up of polysaccharides, proteins, and extracellular DNA effectively limiting the solubility of nanomaterials and thus their bioavailability. Zang et al. (2024) reported that Ag NPs can become incorporated within EPS layers and therefore have a reduced capability to penetrate bacterial cell membranes or to stimulate oxidative stress. EPS not only captures nanomaterials but can also reduce their biocidal activity by binding reactive species, including metal ions and reactive oxygen species (ROS).

QS is significantly involved in managing microbial surface protection against nanomaterials. QS enables microbial populations to coordinate the production of surface-modifying molecules, including EPS and specific enzymes that degrade or deactivate nanomaterials. It was reported that QS-regulated resistance is particularly effective in biofilm-forming bacteria, as the collective action of the population enhances the robustness of the surface barriers (Afrasiabi and Partoazar, 2024).

As a result, researchers have looked for highly elaborated solutions to the problem of nanomaterial design. It has proved possible to couple nanoparticles with peptides or antibodies for delivery past the microbial surface and the coating has demonstrated an ability to release the drug payload once it locates and binds to the microbial cell surface receptors or enzymes. Li et al. (2024) suggested employing stimuli-triggered nanoparticles effective at certain conditions within the biofilm, like low pH or enzymes, to better enter the EPS layers. Innovative approaches also include hybrid nanoparticles with dual functionalities, such as photothermal or photodynamic effects, which disrupt microbial surfaces by generating localized heat or ROS. Others emphasized that such multifunctional nanoparticles could overcome surface modifications by physically or chemically destabilizing microbial barriers, enhancing their antimicrobial efficacy (Sedighi et al., 2024).

5. Challenges in nanomaterial-based antimicrobial therapies

While Sections 2–4 establish what antimicrobial nanomaterials are, how they are used, and why they work, this section focuses on the practical constraints (safety, delivery, regulation, and manufacturability) that determine whether these technologies can be translated into real-world antimicrobial therapies.

5.1. Toxicity and biocompatibility issues

Antibacterial therapies (primarily antibacterial) employing nanomaterials have been described as a major advancement in dealing with emerging resistant pathogens. However, the essential problems which have grown along with these advancements are toxicity and biocompatibility issues. A synthesis of the existing literature points to the complex interactions that exist between the concept of antimicrobial efficacy and the need to promote the overall safety of human life as well as that of the environment.

Nanomaterials are characterized by being very small and possessing a highly reactive surface on account of which they possess special antimicrobial characteristics. Nevertheless, the said properties contribute to cytotoxicity in human cells of a given tissue. ROS production is another important pathway through which nanoparticles produce antimicrobial effects, although this mechanism also contributes to cytotoxicity to mammalian cells. It was observed that the AgNPs have broad-spectrum microbial activity exhibiting cytotoxicity to epithelial and immune cell types by causing oxidative stress, mitochondrial dysfunction, and apoptotic cell death near the therapeutic concentration (Barua and Buragohain, 2024). Others have also described that treatment with titanium dioxide nanoparticles (TiO_2 NPs) can provoke inflammatory reactions and enhance tissue injury (Ziental et al., 2020). Thus, the safety profile of nanomaterials highlights that they are double-edged and require appropriate dosing and targeting strategies.

Biocompatibility challenges also arise from the impact of nanoparticles on the microbial flora or the human associated microbial communities. It is firmly established that microbiomes contribute to homeostasis, and any imbalance, including dysbiosis, secondary infections, and metabolic abnormalities, may occur. So, the antimicrobial nanomaterials that are capable of eliminating a wide range of pathogens affect the beneficial microbial community, which has long-term effects on host health (Ogunsona et al., 2020). Also, the constant application of nanoparticles has been linked with development of resistant microbial strains thus increasing the antimicrobial resistance worldwide (Mba and Nweze, 2021).

In recent years, the environmental concern of nanomaterial-based therapies has emerged as a significant concern. Nanomaterials that are emitted in the environment can find their way into water bodies and eventually into the soils hence interfere with the balances of ecosystems. For instance, it was reported that both silver and zinc oxide nanoparticles concentrations in organisms and induce oxidative stress at non-lethal concentrations (Mahjoubian et al., 2023). However, their stability in the environment also poses long-term toxicity issues for these materials and their biomagnification in the food chain. Solving these challenges requires efforts to develop new strategies for the design of nanomaterials. For example, the nanoparticles can be coated with biocompatible polymers, polyethylene glycol (PEG) to reduce cytotoxicity while maintaining antimicrobial activity (Ibne Shoukani et al., 2024). Others referred to stimuli-responsive nanomaterials that are triggered under particular circumstances, e.g., changes in pH or action of enzymes, thus sparing health tissues and microbiomes (Scott et al., 2022).

Nevertheless, some compliance and safety evaluation issues are still present in the current system. Such measures include the development of standardized protocols for the assessments of pharmacokinetics and biodistribution, and toxic effects in the environment of nanomaterials. Moreover, safety, sustainability, and efficacy should be incorporated in compliance with effective nanomaterial-based antimicrobials' deployment.

5.2. Delivery challenges and target specificity

Nanomaterials are generally effective in antimicrobial therapies, but their delivery and targeting remain major challenges. Although nanomaterials have broad-spectrum activity against microbes, they cannot selectively damage pathogens without affecting host tissues. The literature suggests that factors related to nanomaterial characteristics, pathogen microniches, and biological opsonization complicate delivery, highlighting the need for smarter approaches to targeting.

Nanomaterials, including, for example, silver nanoparticles (AgNPs), have a broad spectrum of antimicrobial activity based on direct and indirect toxic effects, including membrane damage and the formation of reactive oxygen species (ROS). Still, such mechanisms are not very selective as they impact both pathogens as well as healthy cells. Girma et al. (2024) also found that the mechanism of action of AgNPs includes bacterial membrane damage, although they also exert genotoxic and cytotoxic effects in mammalian cells through oxidative stress and apoptosis. Titanium dioxide nanoparticles (TiO_2 NPs) also have wide-spectrum antibacterial properties when activating under UV light; however, they also harm the host tissues *in vivo* applications. These make them rather non-specific not only from the clinical standpoint but also safety-wise.

Several barriers continue to limit effective nanomaterial delivery to infected tissues. A major challenge is the complexity and heterogeneity of microbial microenvironments, as many pathogens reside in niches characterized by low pH, limited oxygen availability, intracellular localization, or biofilm formation. These conditions can restrict nanoparticle penetration, alter nanomaterial stability, and reduce antimicrobial activity at the site of infection. According to Li et al. (2024) biofilms are chemical defenses that greatly limit the capacity and function of nanoparticles. This limited penetration can lead to attainment of subtherapeutic concentrations in the infected site hence increasing the risk of bacterial resistance and poor therapeutic efficacy. The other major challenge is that several nanomaterials use passive targeting mechanisms to avoid targeting diseased cells accurately. The passive targeting based on EPR is more suitable for cancer therapy but unsuitable for microbial infections due to the lack of proper vascular architecture for EPR-mediated accumulation (Joseph et al., 2023). Consequently, nanomaterials tend to deposit to non-target tissues further enhancing the systemic toxicity and reducing pathogen-targeted effects.

In response to these limitations, there have been studies towards trying to improve targeting specificity. Decorating nanomaterials with targeting ligands including antibody, peptides, and aptamer could enhance pathogen recognition. Kosikowska-Adamus et al. (2024) proved that gold nanoparticles with antimicrobial peptides exhibit minimal non-specific binding to the bacterial cells due to smooth surface of bacterial cell walls. Another class of smart materials involves stimuli-responsive nanomaterials or nanoparticles that can undergo particular conformational changes in response to specific environment conditions e.g. pH or enzyme presence. These materials remain inactive until they reach a particular environment in the site of infection, which helps to reduce side effects (Summer et al., 2024).

Liposomes and polymeric nanoparticles, for instance, can be regarded as solutions to these challenges of drug delivery systems. Such carriers allow gradual liberation of antimicrobial agents at the site of infection and, thus, minimize systemic effects together with maximum pathogen specificity. However, challenges such as scalability, stability, and cost do not make them popular (Moreno and Sipponen, 2024).

5.3. Regulatory and safety concerns

The escalation of antibiotic resistance has driven the development of

nanotechnology-based systems that offer innovative strategies in antimicrobial treatments. However, clinical application of these therapies is challenged by several factors, many of which stem from regulatory and safety issues related to nanomaterials that differentiate them from traditional drugs. These issues include toxicity, environmental consequences and practical difficulties associated with setting uniform legal standards for such new material.

One of the greatest difficulties in addressing nanomaterials regulation is the absence of clear rules, taking into consideration the variation of the physicochemical properties of nanoparticles by size, shape, surface charge, or composition. Older regulations mostly developed for conventional drugs do not take these attributes into account even though these properties greatly determine the behavior of nanoparticles in the body. For example, the US Food and Drug Administration (FDA) and European Medicine Agency (EMA) have provided some general recommendations on nanomaterials; nevertheless, these guidelines are insufficient and not adapted to the challenges of nanomaterial risk assessment (Malik et al., 2023). Hence, the current regulations deal with the chemical characterization of nanomaterials and do not constitute the crucial elements of their interactions with biology. These failures are visible in the ill-defined descriptions of nanoparticle behavior *in vivo*, including biodistribution, toxicity, and nanoparticle persistence in tissues (Kumar et al., 2023).

Potential toxicity is still a critical issue that should be faced while applying nanomaterials in clinical practice. The features, which are responsible for the antimicrobial action of NPs, such as size and surface area, enhance the ability of NPs to provoke reactivity, oxidative stress, and cellular membrane damage. This creates the question of whether cytotoxicity and organ damage can occur, especially if the nanomaterials tend to accumulate in tissues like liver, kidneys, and lungs (Fujihara and Nishimoto, 2023). Silver and gold nanoparticles also cause inflammation in the mammalian cell and lead to apoptotic and necrotic forms of cell death that further challenge any clinical use (Adewale et al., 2024). However, regulatory institutions have not provided stringent or uniform guidelines for the determination of nanotoxicity thus creating unknown factors on the appropriate dosage and long-term impacts.

Apart from the potential toxicity to humans, there are other issues which have lately been of worry, especially the effects on the environment of nanomaterials. The nanoparticles once they are emitted in the environment can cause unpredictable effects on the ecosystems. Because of their small size and high reactivity, they significantly accumulate in living organisms' tissues and are toxic to both water and land creatures. Shukla et al. (2024) pointed out that if nanomaterials entered water systems, then it would make changes to microbial ecosystems which may have unanticipated environmental impacts. Nevertheless, the main regulatory bodies, including the Environmental Protection Agency (EPA), still lack specific and coherent standards for evaluating the environmental consequences of nanomaterials, especially when used in antimicrobial systems. This lack of regulation still prompts some important concerns regarding the life cycle of nanomaterials and their implication as eventual contributors to environmental degradation.

Another challenge associated with nanomaterials used in antimicrobial therapies is that the products are not standard and their manufacturing involves batch variability. Nanomaterial fabrication processes are intricate, and thus, the nanoparticles featured in this study can vary in size, morphology, and stability. These relate to the aspects that raise the level of difficulty in attaining compliance to the set regulatory approval standards as well as hindering the easy execution of standardization. Compared with traditional pharmaceuticals, nanomaterials may not undergo the same extent of quality control in manufacturing and production, therefore whether one can confidently reproduce the dosing, administration, and outcome of a therapeutic or diagnostic nanomaterial is questionable.

In response to these challenges, scholars have called for more specific and harmonized regulatory frameworks to govern the use of nanomaterials. The development of such guidelines will require coordinated international collaboration among regulatory agencies, industry, and research institutions, supported by advanced methods for nanomaterial characterization and risk assessment (Bleeker et al., 2023). Achieving more robust nanotoxicological evaluation will also depend on the systematic use of nanotoxicology data, standardized risk-assessment procedures, and effective post-market surveillance to support the safe and successful application of nanomaterials in antimicrobial therapies.

5.4. Economic challenges of mass-producing nanomaterials for antimicrobial use

The use of nanomaterials and the possibility of their fast and efficient growth is well documented in literature. Nevertheless, due to the high surface area, increased reactivity of nanomaterials, and broad spectrum of antimicrobial activity, the problem of high cost of large-scale production of nanomaterials and its commercialization acts as a significant limitation. These challenges as identified by a literature review on past work are as a result of a number of factors which include; the synthesis methods which are complex, the cost of the raw materials which is relatively high, specialized manufacturing technologies used in the process, not forgetting the rate of increase of regulatory measures which have an effect on the time taken to produce the product and the cost of production.

A recent study identified some of the factors that hinder the commercialization of nanomaterials as; high cost and challenging synthesis mechanisms. Chemical and physical synthesis methods such as CVD, sol-gel and laser ablation are most efficient in preparations of nanoparticles with specific properties and qualities. However, they frequently involve high cost of reagents, instruments, and power, so impractical for industrial use (Iravani et al., 2014). Chemical techniques, for instance, use hazardous solvents and chemical reagents all of which add to the overall costs of production in addition to posing risks to the environment. Moreover, these methods also provide limited quantities of nanoparticles, and hence supposing that voluminous quantities of nanoparticles will be required for commercial uses (Nyabadza et al., 2023).

To overcome these problems, there has been growing concern towards the development of other methods, including the so-called "green synthesis'' employing bio or plant-mediated methods. These techniques present a clear path for the attainment of a sustainable and cheap process through employing naturally available materials and avoiding or minimizing the use of hazardous chemicals (Syed et al., 2026). Nevertheless, the use of such green methods still poses a challenge in terms of its scalability. The findings have postulated that although green synthesis is cheaper in terms of cost for small scale production, the process has limitations in terms of high precision that is relativity to large scale production. Altogether, these methods though having shown potential are still far from being used for large-scale synthesis of antimicrobial nanomaterials.

Fluctuations in the cost of these raw materials add another dimension which puts a lot of pressure on companies producing nanomaterial since their cost is relatively high. Nanomaterials tend to utilize noble metals including silver, gold, and platinum, where they are expensive, as well as volatile in price (Demishkevich et al., 2023). Silver nanoparticles are used extensively for their antimicrobial characteristics; however, their costs are highly volatile because of the dependence on mining and supply chains. Co-ordination of costs over time becomes challenging thus making it challenging to effectively and sustainably introduce nanomaterial-based products, or even sustain businesses based on these products or services. Furthermore, even though carbon nanotubes or silica nanoparticles have been proposed as cheaper CNT substitutes, the lower-cost materials are also not easy to synthesize, control the quality of, or functionalize (Altaf et al., 2026).

High costs linked with building additional manufacturing facilities

that can accommodate nanomaterial production heighten the economic barriers to scaling up. Nanomaterials involve complex and often capital-intensive synthesis processes that need specialized equipment in electron microscopes, high-pressure reactors and computer-controlled systems for quality check, all of which are capital-intensive (Kar et al., 2025). These facilities are costly to develop since they demand special infrastructure, and the management of such facilities demands professional labor, which makes the operational costs very high. The requirement for uniformity and biocompatibility in the forms and properties of nanomaterials used for antimicrobial purposes is another layer of cost. These financial requirements hold back the growth of the smaller manufacturers, thus having less capability than the larger corporations to bear these costs.

Regulation can be considered as one of the major barriers, which has an impact on the possibility to produce antimicrobial nanomaterials of high demand among the broad population in a cost-effective manner. Due to their relatively recent introduction to the market, nanomaterials attract much attention from the legislative bodies, specifically in the biomedical and health care segment. The safety, effectiveness, and effects of nanomaterials on the environment and health are only confirmed after the nanomaterials have been subjected to strict laboratory and safety evaluations which are resource and time consuming and demand the availability of appropriate test facilities (Ma et al., 2024). In addition, there is no one standard regulatory approach across the globe when it comes to regulating nanomaterials; they must deal with a multitude of regulations in different regions and countries that have different requirements and guidelines in terms of approval of nanomaterials (Allan et al., 2021). These regulatory complexities delay market entry and increase development costs, further hindering the scalability of nanomaterial production.

5.5. Economic, sustainability, and clinical translation challenges

While the therapeutic potential of nanomaterials for mitigating AMR has been extensively demonstrated *in vitro* and in preclinical models, their clinical translation remains constrained by significant economic, regulatory, and sustainability challenges. One of the primary economic barriers is the high cost of raw materials required for GMP-compliant production of nanomedicines. Many functional nanomaterials, including lipid nanoparticles (LNPs), liposomes, and metal-based nanoparticles, rely on high-purity precursors such as specialty lipids, surfactants, or metallic salts, which are limited in supply and commercially expensive. The cost of these raw materials is further amplified when synthesis must meet stringent pharmaceutical-grade standards, a requirement for clinical use (Hussain et al., 2024).

Beyond raw materials, the manufacturing process itself represents a substantial financial burden. Injectable and implantable nanomedicines necessitate aseptic, sterile production environments with validated cleanrooms, sterilization protocols, and sterile fill-finish capabilities—these facilities require considerable capital investment, ongoing operational expenditure, and highly trained personnel. Additionally, multi-step batch or continuous processes for nanomaterial synthesis often exhibit non-linear scale-up characteristics, meaning that laboratory-optimized methods cannot always be directly translated to industrial production without redesign and process validation.

Indeed, manufacturing immaturity underlines this challenge: as one review of lipid-based nanomedicines notes, “manufacture remains immature, and challenges exist on an industrial scale due to high batch-to-batch variability (Osouli-Bostanabad et al., 2022). Failures in scale-up have historically led to product shortages, for example in the case of pegylated liposomal doxorubicin (Doxil) where manufacturing-related bottlenecks caused supply interruptions, this case underscores the vulnerability of complex nanomedicine supply chains and highlights the importance of redundant manufacturing capacity and process standardization.

In addition to these cost-related considerations, rigorous quality control and analytical characterization requirements contribute substantially to the overall economic burden. Nanomedicines demand comprehensive physicochemical characterization, including particle size distribution, polydispersity index, surface charge, encapsulation efficiency, and stability under physiologically relevant conditions. Each batch must undergo validated release testing to ensure consistency and compliance with regulatory standards. These quality control requirements necessitate specialized analytical equipment and trained personnel, further raising operational expenditures. Regulatory obligations compound these challenges. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) currently assess nanomedicines on a case-by-case basis, with no unified regulatory pathway for all classes of nanomaterials. This evaluation often necessitates additional non-clinical studies including ADME assessments, toxicology, and environmental fate evaluations to address concerns about nanoparticle biodistribution, persistence, and off-target effects (Allan et al., 2021). The absence of standardized regulatory guidelines increases uncertainty, extends development timelines, and escalates costs, creating an inherent risk for developers seeking to advance nanomaterials into clinical use. Intellectual property considerations can also impede translation, as key enabling technologies such as proprietary LNP formulations are frequently protected by patents, requiring licensing agreements or complex freedom-to-operate analyses that further add to time and cost burdens.

Real-world case studies illustrate both the potential for scalable nanomedicine production and the associated challenges. The recent global scale-up of LNP-based mRNA vaccines exemplifies the capacity to achieve high-volume, cost-efficient production under exceptional circumstances. Through deployment or high-throughput mixing systems, downstream ethanol removal, and GMP-compatible fill-finish operations, manufacturers successfully expanded production across unprecedented scales (Hussain et al., 2024; Ahl, 2025). However, this success was predicated on unprecedented demand, existing supply chains, and heavy public investment conditions rarely present for antimicrobial nanomedicines. Conversely, products like pegylated liposomal doxorubicin (Doxil) highlight the fragility inherent in traditional liposomal manufacturing, where batch variability and limited manufacturing sites contributed to acute shortages, necessitating regulatory intervention and importation of alternatives (Barlas, 2013; Gabizon et al., 2025). These contrasting examples underscore the importance of early design-for-manufacture strategies, the implementation of redundant production sites, and the prioritization of scalable, reproducible processes to reduce supply-chain vulnerability.

Sustainability considerations present an additional layer of complexity for the clinical translation of antimicrobial nanomaterials. Metal-based nanoparticles, particularly AgNPs employed in wound dressings, coatings, and topical antimicrobial formulations, exhibit broad-spectrum antimicrobial activity but pose environmental and ecological risks. AgNPs readily transform in wastewater, accumulate in sludge, and have potential to disrupt microbial communities and aquatic ecosystems; the environmental fate of these materials must therefore be addressed in life-cycle assessments (Elbehiry and Abalkhail, 2025; Faghani and Azarniya, 2024). Moreover, the use of organic solvents, reducing agents, and energy-intensive synthesis steps in many nanomaterial production methods generates hazardous waste and increases the carbon footprint, requiring the adoption of greener synthesis routes, solvent recovery systems, and continuous flow processes to improve sustainability. Some nanomedicines, such as LNP formulations, require stringent cold-chain storage which adds to operational costs and raises questions of distribution equity in low-resource settings (Hasan et al., 2026).

Given these multifaceted challenges, the translation of nanomaterials for antimicrobial applications demands strategic foresight in research and development. Early incorporation of scalable, solvent-minimizing synthesis techniques, continuous manufacturing platforms, and microfluidic processing can markedly reduce both CAPEX and per-

unit costs while improving reproducibility (Bi et al., 2025). Engaging regulatory authorities early and using available nanomedicine reflection papers and concept guidelines can streamline approval pathways, focus pre-clinical testing and reduce regulatory uncertainty. Explicit consideration of environmental impact, including wastewater fate, bioaccumulation and energy use, should be integrated into both preclinical studies and manufacturing planning to ensure long-term sustainability. Finally, robust economic modelling incorporating facility build-out, operational costs, material usage, and potential per-unit production cost can guide realistic budgeting and investment decisions, particularly for nanomaterials targeting lower-income markets where affordability and access are critical.

In conclusion, while nanomaterials offer transformative potential in addressing antimicrobial resistance, their successful clinical translation is contingent upon overcoming substantial economic, regulatory, and sustainability barriers. Lessons from existing nanomedicine products demonstrate that mass production is feasible under favorable conditions of demand, investment, and regulatory engagement, yet many antimicrobial-focused nanomaterials remain vulnerable to cost, scale-up and ecological challenges. Therefore, a comprehensive, integrated approach encompassing manufacturability, regulatory planning, lifecycle assessment, and supply-chain resilience is essential to realize the promise of nanomaterials as effective, clinically translatable, and environmentally responsible antimicrobials.

6. Future directions and emerging strategies

6.1. Development of smart and responsive nanomaterials

The advancement of antimicrobial nanotechnology is increasingly focused on the design of stimuli-responsive nanomaterials capable of precise, on-demand activation in response to specific biological triggers such as pH fluctuations, enzymatic activity, temperature variations, or ROS levels at infection sites. These intelligent systems aim to maximize therapeutic efficacy while minimizing off-target toxicity, addressing a critical limitation of conventional antimicrobial approaches. Recent innovations include the development of pH-responsive silver nanoparticles that selectively release antimicrobial ions in acidic microenvironments typical of infections, and enzyme-activated nanozymes that catalyze the generation of ROS specifically within bacterial biofilms, enhancing localized antimicrobial action (Feng et al., 2025; Ullah et al., 2026).

6.2. Nanomaterial design for overcoming resistance mechanisms

Given the evolving resistance mechanisms of microbial pathogens, the rational engineering of nanomaterials to bypass or neutralize microbial defenses is paramount. Current strategies emphasize tailoring nanomaterial attributes such as shape (e.g., rods, stars, sheets), size (preferably $<$10 nm for improved tissue penetration and biofilm infiltration), and surface chemistry (e.g., cationic functionalization or zwitterionic modifications) to enhance antimicrobial activity and minimize immune evasion. Advanced approaches involve utilizing sharp-edged nanostructures like graphene derivatives to physically disrupt bacterial membranes, alongside multimodal nanomaterials that integrate photothermal, photodynamic, and ion-releasing functionalities, effectively overwhelming microbial adaptive responses (Goshisht et al., 2025).

6.3. Nanomaterial-based vaccines and immune modulation

Nanotechnology is reshaping the landscape of infectious disease prevention through the development of nanomaterial-based vaccines and immune-modulating platforms. Owing to their tunable physicochemical properties, nanomaterials serve as efficient carriers for antigens, promoting enhanced antigen presentation, controlled antigen release, and targeted delivery to immune cells such as dendritic cells, thereby augmenting immunogenicity.

Recent advancements highlight the use of lipid–polymer hybrid nanoparticles for the delivery of bacterial antigens, significantly boosting host immune responses (Li et al., 2025), as well as nano-adjuvants that activate innate immune pathways, such as the STING (stimulator of interferon genes) pathway, offering robust and sustained protection against multidrug-resistant pathogens (Xu et al., 2024).

6.4. Integration with emerging technologies

The convergence of nanotechnology with artificial intelligence (AI), machine learning (ML), and computational modeling is transforming the design and functional optimization of antimicrobial nanomaterials. Emerging AI/ML platforms facilitate high-throughput screening, prediction of nanomaterial–pathogen interactions, and data-driven optimization of synthesis parameters, accelerating the discovery of next-generation antimicrobial agents (Jyakhwo et al., 2025; Dhaarani and Reddy, 2025). Moreover, the integration of nanomaterials into biosensing technologies enables real-time, ultra-sensitive detection of AMR genes and pathogenic organisms, paving the way for rapid, point-of-care diagnostic tools critical for early intervention (Taha et al., 2025).

6.5. Sustainable and eco-friendly nanomaterial solutions

In response to escalating environmental and health concerns, significant efforts are being directed toward the green synthesis of nanomaterials and the development of biodegradable, eco-friendly platforms. Methods employing plant extracts, biopolymer matrices (such as chitosan and alginate), and microbial biosynthesis are gaining prominence for the sustainable production of antimicrobial nanostructures.

New material classes, including biodegradable metal–organic frameworks (MOFs), cellulose nanofibers, and silk fibroin nanoparticles, have demonstrated potent antimicrobial efficacy coupled with favorable biocompatibility and environmental degradability, offering promising alternatives to conventional, non-biodegradable nanomaterials (Goshisht et al., 2025; Huang et al., 2024).

6.6. Clinical translation and real-world applications

Despite the significant progress achieved in laboratory and preclinical studies, the clinical translation of antimicrobial nanomaterials remains in its nascent stages. Nevertheless, a growing number of candidates—particularly nanoparticle-based antimicrobial coatings for medical devices such as catheters and wound dressings—are progressing through Phase I/II clinical trials (Feng et al., 2025). Key challenges impeding broader clinical adoption include issues related to scalability, batch-to-batch reproducibility, long-term biocompatibility and safety, and the complexities of regulatory approval. To navigate these hurdles, collaborative strategies involving industrial partnerships, adaptive clinical trial designs, and early engagement with regulatory agencies are being increasingly advocated to facilitate the successful commercialization and integration of nanomaterial-based antimicrobials into healthcare systems (Rodríguez-Gómez et al., 2025).

7. Conclusion

The increasing prevalence of AMR presents a significant threat to global health, requiring innovative therapeutic strategies beyond traditional antibiotics. This review has emphasized the progress made in nanomaterial-based methods, such as metal and metal oxide nanoparticles, carbon-based nanostructures, polymeric systems, lipid-based carriers, and hybrid platforms. These materials offer diverse antimicrobial mechanisms, spanning membrane disruption, oxidative stress induction, biofilm inhibition, and intracellular interference that together address many limitations of conventional drugs.

Despite these advancements, significant challenges still impede clinical translation. Key issues include: (i) toxicity and biocompatibility concerns, which necessitate balancing antimicrobial effectiveness with host safety; (ii) manufacturing and scalability hurdles, as many complex nanomaterials lack cost-effective, reproducible production methods; (iii) regulatory uncertainty, since existing frameworks are inadequately equipped to assess nanomaterials with multifunctional or stimulus-responsive characteristics; and (iv) emerging microbial adaptations, including biofilm reinforcement and efflux responses, that require proactive design strategies. To expedite progress, several high-impact directions should be emphasized. First, regulatory reform is essential to create standardized evaluation protocols for nanomaterial safety, pharmacokinetics, and long-term biodistribution, which would help alleviate approval bottlenecks. Second, sustainable design should be a core principle, focusing on biodegradable, green-synthesized nanomaterials that reduce ecological impact while ensuring efficacy. Third, translational pipelines need enhancement through partnerships between academia and industry that merge early-stage mechanistic insights with large-scale production, toxicology, and clinical trial design. Fourth, adaptive and smart nanomaterials, including stimuli-responsive systems and combination platforms should be developed to combat evolving resistance mechanisms. Lastly, policy-level initiatives that encourage investment in antimicrobial nanotechnology and facilitate coordinated global monitoring of resistance patterns will be vital.

Overall, while nanotechnology holds transformative potential in the battle against AMR, its effectiveness hinges on addressing concrete scientific, regulatory, and translational challenges. A strategic emphasis on safety, sustainability, and clinical integration can help propel nanomaterials from promising laboratory innovations to effective front-line solutions against drug-resistant infections.

Ethical approval

Not applicable.

Disclosure statement on generative AI use

We confirm that an appropriate disclosure statement has been included in the manuscript. Generative AI tools were not used in the generation, analysis, interpretation of data, or preparation of figures. Any use of AI-assisted tools, if applicable, was limited to language editing and improving readability, and all content was carefully reviewed and verified by the authors, who take full responsibility for the accuracy and integrity of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Abdel-Raouf, N., Al-Enazi, N.M., Ibraheem, I.B.M., 2017. Green biosynthesis of gold nanoparticles using Galaxaura elongata and characterization of their antibacterial activity. Arab. J. Chem. 10, S3029–S3039. https://doi.org/10.1016/J.ARABJC.2013.11.044.

Adewale, O.B., Anadozie, S.O., Davids, H., Roux, S., 2024. Potential therapeutic role of gold nanoparticles in inflammatory diseases. Gold Nanoparticl Drug Delivery. https://doi.org/10.1016/b978-0-443-19061-2.00021-3.

Aflakian, F., Mirzavi, F., Aiyelabegan, H.T., Soleimani, A., Gholizadeh Navashenaq, J., Karimi-Sani, I., Rafati Zomorodi, A., Vakili-Ghartavol, R., 2023. Nanoparticles-based therapeutics for the management of bacterial infections: a special emphasis on FDA approved products and clinical trials. Eur. J. Pharmaceut. Sci. 188, 106515. https://doi.org/10.1016/J.EJPS.2023.106515.

Afrasiabi, S., Partoazar, A., 2024. Targeting bacterial biofilm-related genes with nanoparticle-based strategies. Front. Microbiol. 15, 1387114. https://doi.org/10.3389/fmicb.2024.1387114.

Agarwal, M., Ganesan, R., Ray Dutta, J., 2026. Functional nanomaterials in combating antimicrobial resistance: innovations in wound dressings and biomedical implants. Nano Trends 13, 100174. https://doi.org/10.1016/J.NWNANO.2025.100174.

Ahl, P.L., 2025. Microfluidic and turbulent mixing for mRNA LNP vaccines. Pharmaceutics 17 (9), 1148. https://doi.org/10.3390/pharmaceutics17091148.

Ahmed, S.F., Mofijur, M., Rafa, N., Chowdhury, A.T., Chowdhury, S., Nahrin, M., Islam, A.B.M.S., Ong, H.C., 2022. Green approaches in synthesising nanomaterials for environmental nanobioremediation: technological advancements, applications, benefits and challenges. Environ. Res. 204, 111967. https://doi.org/10.1016/j.envres.2021.111967.

Ahmed, S.K., Hussein, S., Qurbani, K., Ibrahim, R.H., Fareeq, A., Mahmood, K.A., Mohamed, M.G., 2024. Antimicrobial resistance: impacts, challenges, and future prospects. J. Med. Surg. Public Health 2, 100081. https://doi.org/10.1016/J.GLMEDI.2024.100081.

Ahmed, T., Noman, M., Manzoor, N., Ali, S., Rizwan, M., Ijaz, M., Allemailem, K.S., BinShaya, A.S., Alhumaydhi, F.A., Li, B., 2021. Recent advances in nanoparticles associated ecological harms and their biodegradation: global environmental safety from nano-invaders. J. Environ. Chem. Eng. 9, 106093. https://doi.org/10.1016/j.jece.2021.106093.

Akbarian, M., Chen, S.-H., Kianpour, M., Farjadian, F., Tayebi, L., Uversky, V.N., 2022. A review on biofilms and the currently available antibiofilm approaches: matrix-destabilizing hydrolases and anti-bacterial peptides as promising candidates for the food industries. Int. J. Biol. Macromol. 219, 1163–1179. https://doi.org/10.1016/j.ijbiomac.2022.08.192.

Al-Marzooq, F., Ghazawi, A., Daoud, L., Tariq, S., 2023. Boosting the antibacterial activity of azithromycin on multidrug-resistant Escherichia coli by efflux pump inhibition coupled with outer membrane permeabilization induced by phenylalanine-arginine β-Naphthylamide. Int. J. Mol. Sci. 24, 8662. https://doi.org/10.3390/ijms24108662.

Alidriss, O.M., AlSudais, H., Alhumaidan, O.S., Altwaijry, H.D., Bakhsh, A., Almuhanna, Y., Alkudmani, Z.S., Alqarni, I.A., Alenazi, D., Aljasham, A.T., Jamous, Y.F., 2025. Targeted drug delivery strategies in overcoming antimicrobial resistance: advances and future directions. Pharmaceutics 17 (11), 1426. https://doi.org/10.3390/pharmaceutics17111426.

Allan, J., Belz, S., Hoeveler, A., Hugas, M., Okuda, H., Patri, A., Rauscher, H., Silva, P., Slikker, W., Sokull-Kluettgen, B., Tong, W., Anklam, E., 2021. Regulatory landscape of nanotechnology and nanoplastics from a global perspective. Regul. Toxicol. Pharmacol. 122, 104885. https://doi.org/10.1016/J.YRTPH.2021.104885.

Alqahtany, M., Khadka, P., Niyonshuti, I., Krishnamurthi, V.R., Sadoon, A.A., Challapalli, S.D., Chen, J., Wang, Y., 2019. Nanoscale reorganizations of histone-like nucleoid structuring proteins in Escherichia coli are caused by silver nanoparticles. Nanotechnology 30, 385101. https://doi.org/10.1088/1361-6528/ab2a9f.

Altaf, N. ul H., Ayyaz, M., Zhang, Y., Shahzad, M., Khan, A., Sanam, Liaqat, W., Ashar, A., Malik, R., Bhutta, Z.A., 2026. Recent advances in the synthesis and processing of carbon nanotubes and carbon nanocomposites for energy storage, biomedical, and environmental applications. ChemistryOpen 15, e202500501. https://doi.org/10.1002/open.202500501.

Amaral, M.N., Kumar, P., Faísca, P., Ferreira, H.A., Coelho, J.M.P., Gaspar, M.M., Reis, C.P., 2025. Gold nanoparticle-mediated photothermal therapy: expanding the frontiers

of cancer treatment and theragnostics. Biomed. Pharmacother. 190, 118399. https://doi.org/10.1016/J.BIOPHA.2025.118399.
Ammendolia, M.G., De Berardis, B., 2022. Nanoparticle impact on the bacterial adaptation: focus on nano-titania. Nanomaterials (Basel) 12 (20), 3616. https://doi.org/10.3390/nano12203616.
Amrhar, R., Singh, J., Eesaee, M., Carrière, P., Saidi, A., Nguyen-Tri, P., 2025. Polymeric nanocomposites-based advanced coatings for antimicrobial and antiviral applications: a comprehensive overview. Results Surf. Interfaces 19, 100497. https://doi.org/10.1016/J.RSURFI.2025.100497.
Anastasiadis, S.H., Chrissopoulou, K., Stratakis, E., Kavatzikidou, P., Kaklamani, G., Ranella, A., 2022. How the physicochemical properties of manufactured nanomaterials affect their performance in dispersion and their applications in biomedicine: a review. Nanomaterials (Basel) 12, 552. https://doi.org/10.3390/nano12030552.
Anes, J., Dever, K., Eshwar, A., Nguyen, S., Cao, Y., Sivasankaran, S.K., Sakalauskaitė, S., Lehner, A., Devineau, S., Daugelavičius, R., Stephan, R., Fanning, S., Srikumar, S., 2021. Analysis of the oxidative stress regulon identifies soxS as a genetic target for resistance reversal in multidrug-resistant Klebsiella pneumoniae. mBio 12 (3), e00867. https://doi.org/10.1128/mbio.00867-21, 21.
Arana, L., Gallego, L., Alkorta, I., 2021. Incorporation of antibiotics into solid lipid nanoparticles: a promising approach to reduce antibiotic resistance emergence. Nanomaterials 11 (5), 1251. https://doi.org/10.3390/nano11051251.
Asokan-Sheeja, H., Das, D., Nguyen, J.N., Xu, J., Mukut, M.T.H., Chau, T.H., Buonomo, J. A., Hong, Y., Dong, H., 2025. pH-Responsive peptide–polymer hydrogel for biofilm disruption. ACS Appl. Bio Mater. 8, 6415–6425. https://doi.org/10.1021/acsabm.5c00897.
Avila, Y.I., Rebolledo, L.P., Leal Santos, N., Rawlins, B., Radwan, Y., Andrade-Muñoz, M., Skelly, E., Chandler, M.R., Andrade, L.N.S., Kim, T.J., Dobrovolskaia, M.A., Afonin, K.A., 2025. Changes in generations of PAMAM dendrimers and compositions of nucleic acid nanoparticles govern delivery and immune recognition. ACS Biomater. Sci. Eng. 11, 3726–3737. https://doi.org/10.1021/acsbiomaterials.5c00336.
Back, P.I., Yu, M., Modaresahmadi, S., Hajimirzaei, S., Zhang, Q., Islam, M.R., Schwendeman, A.A., La-Beck, N.M., 2024. Immune implications of cholesterol-containing lipid nanoparticles. ACS Nano 18, 28480–28501. https://doi.org/10.1021/acsnano.4c06369.
Balaure, P.C., Niculescu, A.G., Anghel, D., Grumezescu, A.M., Alberts, A., 2025. Role of silver nanoparticles in wound healing: mechanisms, efficacy, and clinical applications. Inorganics (Basel). https://doi.org/10.3390/inorganics13120401.
Barlas, S., 2013. FDA strategies to prevent and respond to drug shortages: finding a better way to predict and prevent company closures. P T 38 (5), 261–263, 2013 May;PMID: 23946619; PMCID: PMC3737981.
Barua, N., Buragohain, A.K., 2024. Therapeutic potential of silver nanoparticles (AgNPs) as an antimycobacterial agent: a comprehensive review. Antibiotics (Basel) 13, 1106. https://doi.org/10.3390/antibiotics13111106.
Bassous, N.J., 2020. Applying Nanotechnology Towards Developing an Integrative Drug Delivery System for Inhibiting antibiotic-resistant Bacteria and Restoring Mitochondrial Genetic Expression in Eukaryotic Host Cells. Northeastern University Library. https://doi.org/10.17760/d20403630.
Bhattacharjee, R., Negi, A., Bhattacharya, B., Dey, T., Mitra, P., Preetam, S., Kumar, L., Kar, S., Das, S.S., Iqbal, D., Kamal, M., Alghofaili, F., Malik, S., Dey, A., Jha, S.K., Ojha, S., Paiva-Santos, A.C., Kesari, K.K., Jha, N.K., 2023. Nanotheranostics to target antibiotic-resistant bacteria: strategies and applications. OpenNano 11, 100138. https://doi.org/10.1016/J.ONANO.2023.100138.
Bi, Y., Xie, S., Li, Z., Dong, S., Teng, L., 2025. Precise nanoscale fabrication technologies, the “last mile” of medicinal development. Acta Pharm. Sin. B 15, 2372–2401. https://doi.org/10.1016/J.APSB.2025.03.040.
Bintang, M.A.K.M., Nopparat, J., Srichana, T., 2025. Assessment of polymyxin B with sodium deoxycholate sulfate micelles in a rat model to combat polymyxin nephrotoxicity. Antibiotics 14. https://doi.org/10.3390/antibiotics14111062.
Birk, S.E., Boisen, A., Nielsen, L.H., 2021. Polymeric nano- and microparticulate drug delivery systems for treatment of biofilms. Adv. Drug Deliv. Rev. 174, 30–52. https://doi.org/10.1016/J.ADDR.2021.04.005.
Bleeker, E.A.J., Swart, E., Braakhuis, H., Fernández Cruz, M.L., Friedrichs, S., Gosens, I., Herzberg, F., Jensen, K.A., von der Kammer, F., Kettelarij, J.A.B., Navas, J.M., Rasmussen, K., Schwirn, K., Visser, M., 2023. Towards harmonisation of testing of nanomaterials for EU regulatory requirements on chemical safety - a proposal for further actions. Regul. Toxicol. Pharmacol. 139, 105360. https://doi.org/10.1016/j.yrtph.2023.105360.
Bonner, J.C., 2011. Carbon nanotubes as delivery systems for respiratory disease: do the dangers outweigh the potential benefits? Expert rev. Respir. Med. https://doi.org/10.1586/ers.11.72.
Boverhof, D.R., Bramante, C.M., Butala, J.H., Clancy, S.F., Lafranconi, W.M., West, J., Gordon, S.C., 2015. Comparative assessment of nanomaterial definitions and safety evaluation considerations. Regul. Toxicol. Pharmacol. 73, 137–150. https://doi.org/10.1016/J.YRTPH.2015.06.001.
Bravo, A.R., Cuevas, M.F., Palavecino, C.E., 2026. Use of antimicrobial photodynamic therapy to inactivate multidrug-resistant enterobacter spp.: scoping review. Drugs and Drug Candidates 5, 28. https://doi.org/10.3390/ddc5020028.
Brown, A.N., Smith, K., Samuels, T.A., Lu, J., Obare, S.O., Scott, M.E., 2012. Nanoparticles functionalized with ampicillin destroy multiple-antibiotic-resistant isolates of Pseudomonas aeruginosa and Enterobacter aerogenes and methicillin-resistant Staphylococcus aureus. Appl. Environ. Microbiol. 78 (8), 2768–2774. https://doi.org/10.1128/AEM.06513-11.
Butler, J., Handy, R.D., Upton, M., Besinis, A., 2023. Review of antimicrobial nanocoatings in medicine and dentistry: mechanisms of action, biocompatibility performance, safety, and benefits compared to antibiotics. ACS Nano 17, 7064–7092. https://doi.org/10.1021/acsnano.2c12488.
Casals, E., Gusta, M.F., Bastus, N., Rello, J., Puntes, V., 2025. Silver nanoparticles and antibiotics: a promising synergistic approach to multidrug-resistant infections. Microorganisms. https://doi.org/10.3390/microorganisms13040952.
Chandra, D.K., Kumar, A., Mahapatra, C., 2025. Smart nano-hybrid metal-organic frameworks: revolutionizing advancements, applications, and challenges in biomedical therapeutics and diagnostics. Hybrid Adv. 9, 100406. https://doi.org/10.1016/J.HYBADV.2025.100406.
Chee, E., García, A.J., 2023. Biomaterial therapeutic strategies for treatment of bacterial lung infections. Biofilm 5, 100111. https://doi.org/10.1016/J.BIOFLM.2023.100111.
Chen, Y., He, X., Chen, Q., He, Y., Chen, F., Yang, C., Wang, L., 2023. Nanomaterials against intracellular bacterial infection: from drug delivery to intrinsic biofunction. Front. Bioeng. Biotechnol. 11, 1197974. https://doi.org/10.3389/fbioe.2023.1197974.
Cho, S., Rasoulianboroujeni, M., Kang, R.H., Kwon, G.S., 2025. From conventional to next-generation strategies: recent advances in polymeric micelle preparation for drug delivery. Pharmaceutics 17 (10), 1360. https://doi.org/10.3390/pharmaceutics17101360.
Coluzzi, C., Guillemet, M., Mazzamurro, F., Touchon, M., Godfroid, M., Achaz, G., Glaser, P., Rocha, E.P.C., 2023. Chance favors the prepared genomes: horizontal transfer shapes the emergence of antibiotic resistance mutations in core genes. Mol. Biol. Evol. 40, msad217. https://doi.org/10.1093/molbev/msad217.
Correa, M.G., Martínez, F.B., Vidal, C.P., Streitt, C., Escrig, J., de Dicastillo, C.L., 2020. Antimicrobial metal-based nanoparticles: a review on their synthesis, types and antimicrobial action. Beilstein J. Nanotechnol. 11, 1450–1469. https://doi.org/10.3762/BJNANO.11.129.
Costabile, G., Mitidieri, E., Visaggio, D., Provenzano, R., Miro, A., Quaglia, F., d'Angelo, I., Frangipani, E., Sorrentino, R., Visca, P., d'Emmanuele di Villa Bianca, R., Ungaro, F., 2022. Boosting lung accumulation of gallium with inhalable nano-embedded microparticles for the treatment of bacterial pneumonia. Int. J. Pharm. 629, 122400. https://doi.org/10.1016/J.IJPHARM.2022.122400.
Crane, J.K., Catanzaro, M.N., 2023. Role of extracellular DNA in bacterial response to SOS-inducing drugs. Antibiotics 12 (4), 649. https://doi.org/10.3390/antibiotics12040649.
Córdova-Espinoza, M.G., González-Vázquez, R., Barron-Fattel, R.R., Gónzalez-Vázquez, R., Vargas-Hernández, M.A., Albores-Méndez, E.M., Esquivel-Campos, A.L., Mendoza-Pérez, F., Mayorga-Reyes, L., Gutiérrez-Nava, M.A., Medina-Quero, K., Escamilla-Gutiérrez, A., 2024. Aptamers: a cutting-edge approach for gram-negative bacterial pathogen identification. Int. J. Mol. Sci. https://doi.org/10.3390/ijms25021257.
Dams, E.T.M., Laverman, P., Oyen, W.J.G., Storm, G., Scherphof, G.L., van der Meer, J. W.M., Corstens, F.H.M., Boerman, O.C., 2000. Accelerated blood clearance and altered biodistribution of repeated injections of sterically stabilized liposomes. J. Pharmacol. Exp. Therapeut. 292 (3), 1071–1079. https://doi.org/10.1016/S0022-3565(24)35391-1.
Das, P., Nath, P.C., Pandey, V.K., Singh, R., Rustagi, S., Shaikh, A.M., Kovács, B., 2025. Carbon quantum dots as emerging biosensors for food safety and environmental applications: advances and challenges. Appl. Food Res. 5, 101255. https://doi.org/10.1016/J.AFRES.2025.101255.
de Oliveira, K.B.S., Leite, M.L., Melo, N.T.M., Lima, L.F., Barbosa, T.C.Q., Carmo, N.L., Melo, D.A.B., Paes, H.C., Franco, O.L., 2024. Antimicrobial peptide delivery systems as promising tools against resistant bacterial infections. Antibiotics 13, 1042. https://doi.org/10.3390/antibiotics13111042.
de Sousa, J.M., Lourenço, M., Gordo, I., 2023. Horizontal gene transfer among host-associated microbes. Cell Host Microbe 31 (4), 513–527. https://doi.org/10.1016/j.chom.2023.03.017.
Demishkevich, E., Zyubin, A., Seteikin, A., Samusev, I., Park, I., Hwangbo, C.K., Choi, E. H., Lee, G.J., 2023. Synthesis methods and optical sensing applications of plasmonic metal nanoparticles made from rhodium, platinum, gold, or silver. Materials (Basel) 16, 3342. https://doi.org/10.3390/ma16093342.
Derakhshi, M., Ashkarran, A.A., Bahari, A., Bonakdar, S., 2018. Shape selective silver nanostructures decorated amine-functionalized graphene: a promising antibacterial platform. Colloids Surf. A Physicochem. Eng. Asp. 545, 101–109. https://doi.org/10.1016/J.COLSURFA.2018.02.031.
Desai, A., Ghosh, S., Sankaranarayanan, S., Bhatia, D., Yadav, A.K., 2025. A one health nanotechnology approach to address antimicrobial resistance: state-of-the-art and strategic outlook. Mater. Adv. 6, 6612–6647. https://doi.org/10.1039/D5MA00487J.
Dey, N., Kamatchi, C., Vickram, A.S., Anbarasu, K., Thanigaivel, S., Palanivelu, J., Pugazhendhi, A., Ponnusamy, V.K., 2022. Role of nanomaterials in deactivating multiple drug resistance efflux pumps – a review. Environ. Res. 204, 111968. https://doi.org/10.1016/j.envres.2021.111968.
Dhaarani, R., Reddy, M.K., 2025. Progressing microbial genomics: artificial intelligence and deep learning driven advances in genome analysis and therapeutics. Intell Based Med., 100251 https://doi.org/10.1016/J.IBMED.2025.100251.
Dizaj, S.M., Lotfipour, F., Barzegar-Jalali, M., Zarrintan, M.H., Adibkia, K., 2014. Antimicrobial activity of the metals and metal oxide nanoparticles. Mater. Sci. Eng. C 44, 278–284. https://doi.org/10.1016/J.MSEC.2014.08.031.
Dove, A.S., Dzurny, D.I., Dees, W.R., Qin, N., Nunez Rodriguez, C.C., Alt, L.A., Ellward, G.L., Best, J.A., Rudawski, N.G., Fujii, K., Czyż, D.M., 2023. Silver nanoparticles enhance the efficacy of aminoglycosides against antibiotic-resistant bacteria. Front. Microbiol. 13. https://doi.org/10.3389/fmicb.2022.1064095.

Du, Y., Lu, J., Guo, X., Xia, Z., Ji, S., 2026. The role of silver and silver-based products in wound management: a review of advances and current landscape. J. Funct. Biomater. 17, 27. https://doi.org/10.3390/jfb17010027.

Dube, E., Okuthe, G.E., 2025. Silver Nanoparticle-based antimicrobial coatings: sustainable strategies for microbial contamination control. Microbiol. Res. (Pavia). https://doi.org/10.3390/microbiolres16060110.

El-Houseiny, W., Mansour, M.F., Mohamed, W.A.M., Al-Gabri, N.A., El-Sayed, A.A., Altohamy, D.E., Ibrahim, R.E., 2021. Silver nanoparticles mitigate aeromonas hydrophila-induced immune suppression, oxidative stress, and apoptotic and genotoxic effects in Oreochromis niloticus. Aquaculture 535, 736430. https://doi.org/10.1016/j.aquaculture.2021.736430.

Elbehiry, A., Abalkhail, A., 2025. Antimicrobial nanoparticles against superbugs: mechanistic insights, biomedical applications, and translational frontiers. Pharmaceuticals 18 (8), 1195. https://doi.org/10.3390/ph18081195.

Fadaei, M.R., Fadaei, M.S., Kheirieh, A.E., Hatami, H., Rahmanian-Devin, P., Tayebi-Khorrami, V., Fathabadi, M.F., Baradaran Rahimi, V., Askari, V.R., 2025. Overview of dendrimers as promising drug delivery systems with insight into anticancer and anti-microbial applications. Int. J. Pharm. X 10, 100390. https://doi.org/10.1016/J.IJPX.2025.100390.

Faghani, G., Azarniya, A., 2024. Emerging nanomaterials for novel wound dressings: from metallic nanoparticles and MXene nanosheets to metal-organic frameworks. Heliyon 10, e39611. https://doi.org/10.1016/J.HELIYON.2024.E39611.

Fahim, M., Shahzaib, A., Nishat, N., Jahan, A., Bhat, T.A., Inam, A., 2024. Green synthesis of silver nanoparticles: a comprehensive review of methods, influencing factors, and applications. JCIS Open 16, 100125. https://doi.org/10.1016/J.JCISO.2024.100125.

Fallah, S., Yusefi-Tanha, E., Peralta-Videa, J.R., 2024. Interaction of nanoparticles and reactive oxygen species and their impact on macromolecules and plant production. Plant Nano Biol. 10, 100105. https://doi.org/10.1016/J.PLANA.2024.100105.

Faseela, P., Joel, J.M., Johnson, R., Janeeshma, E., Sameena, P.P., Sen, A., Puthur, J.T., 2024. Paradoxical effects of nanomaterials on plants: phytohormonal perspective exposes hidden risks amidst potential benefits. Plant Physiol. Biochem. 210, 108603. https://doi.org/10.1016/j.plaphy.2024.108603.

Feng, S., Wang, Zhaoxun, Zhang, Y., Mei, L., Wang, Zhenxing, 2025. Harnessing nanozymes as next-generation antimicrobial agents: from mechanisms to therapeutic strategies. Mater. Today Bio 35, 102499. https://doi.org/10.1016/J.MTBIO.2025.102499.

Fujihara, J., Nishimoto, N., 2023. Review of zinc oxide nanoparticles: toxicokinetics, tissue distribution for various exposure routes, toxicological effects, toxicity mechanism in mammals, and an approach for toxicity reduction. Biol. Trace Elem. Res. 202, 9–23. https://doi.org/10.1007/s12011-023-03644-w.

Fujii, J., Homma, T., Osaki, T., 2022. Superoxide radicals in the execution of cell death. Antioxidants 11 (3), 501. https://doi.org/10.3390/antiox11030501.

Fulindi, R.B., Rodrigues, J.D., Barbosa, T.W.L., Garcia, A.D.G., La Porta, F.A., Pratavieira, S., Chiavacci, L.A., Junior, J.P.A., da Costa, P.I., Martinez, L.R., 2023. Zinc-based nanoparticles reduce bacterial biofilm formation. Microbiol. Spectr. 11 (2), e0483122. https://doi.org/10.1128/spectrum.04831-22.

Gabizon, A.A., Gabizon-Peretz, S., Modaresahmadi, S., La-Beck, N.M., 2025. Thirty years from FDA approval of pegylated liposomal doxorubicin (Doxil/Caelyx): an updated analysis and future perspective. BMJ Oncol. 4, e000573. https://doi.org/10.1136/bmjonc-2024-000573.

Gaikwad, S.S., Warule, S.S., Babar, M.D., Pardeshi, S.K., Dahiwale, S.S., More, M.A., 2026. Facile synthesis of Cu2O-rGO nanocomposite with enhanced electrochemical performance as a supercapacitor electrode. Next Mater. 10, 101430. https://doi.org/10.1016/J.NXMATE.2025.101430.

Gan, W.K., Liew, H.S., Pua, L.J.W., Ng, X.Y., Fong, K.W., Cheong, S.L., Liew, Y.K., Low, M.L., 2022. Novel Cu(II) schiff base complex combination with polymyxin B/Phenylalanine-Arginine β-Naphthylamide against various bacterial strains. Int. J. Pept. Res. Therapeut. 28. https://doi.org/10.1007/s10989-021-10358-x.

Gao, H., Zhao, R., Ye, J., Zhan, M., Yu, R., 2024. Enhancement of biological nitrogen removal system resilience to chronic exposure of zinc oxide nanoparticles by quorum sensing modulation: physiochemical, microbial, and metabolic insights. Bioresour. Technol. 408, 131136. https://doi.org/10.1016/j.biortech.2024.131136.

Garcia, Í.R., de Oliveira Garcia, F.A., Pereira, P.S., Coutinho, H.D.M., Siyadatpanah, A., Norouzi, R., Wilairatana, P., de Lourdes Pereira, M., Nissapatorn, V., Tintino, S.R., Rodrigues, F.F.G., 2022. Microbial resistance: the role of efflux pump superfamilies and their respective substrates. Life Sci. 295, 120391. https://doi.org/10.1016/j.lfs.2022.120391.

Gaurav, A., Bakht, P., Saini, M., Pandey, S., Pathania, R., 2023. Role of bacterial efflux pumps in antibiotic resistance, virulence, and strategies to discover novel efflux pump inhibitors. Microbiology 169 (5). https://doi.org/10.1099/mic.0.001333.

Ghawanmeh, A.A., 2024. Polymeric nanoparticles delivery circumvents bacterial resistance to ciprofloxacin. DARU 32, 455–459. https://doi.org/10.1007/s40199-023-00498-4.

Ghosh, S., Sinha, S.N., 2025. Insights into synergistic antibacterial effects, antioxidant potential, and anticancer activities of green-synthesized silver nanoparticles from Odontosoria chinensis leaves. Next Nanotechnology 8, 100316. https://doi.org/10.1016/J.NXNANO.2025.100316.

Giannakara, M., Koumandou, V.L., 2022. Evolution of two-component quorum sensing systems. Access Microbiol. 4, 303. https://doi.org/10.1099/acmi.0.000303.

Girma, A., Alamnie, G., Bekele, T., Mebratie, G., Mekuye, B., Abera, B., Workineh, D., Tabor, A., Jufar, D., 2024. Green-synthesised silver nanoparticles: antibacterial activity and alternative mechanisms of action to combat multidrug-resistant bacterial pathogens: a systematic literature review. Green Chem. Lett. Rev. 17. https://doi.org/10.1080/17518253.2024.2412601.

Godoy-Gallardo, M., Eckhard, U., Delgado, L.M., de Roo Puente, Y.J.D., Hoyos-Nogués, M., Gil, F.J., Perez, R.A., 2021. Antibacterial approaches in tissue engineering using metal ions and nanoparticles: from mechanisms to applications. Bioact. Mater. 6, 4470–4490. https://doi.org/10.1016/J.BIOACTMAT.2021.04.033.

Goodarzi, S., Da Ros, T., Conde, J., Sefat, F., Mozafari, M., 2017. Fullerene: biomedical engineers get to revisit an old friend. Mater. Today 20, 460–480. https://doi.org/10.1016/J.MATTOD.2017.03.017.

Goshisht, M.K., Goshisht, A., Bajpai, Animesh, Bajpai, Abhishek, 2025. Recent advances in biomedical applications of smart nanomaterials: a comprehensive review. RSC Pharm. 2, 1227–1267. https://doi.org/10.1039/D5PM00137D.

Graves Jr., J.L., Tajkarimi, M., Cunningham, Q., Campbell, A., Nonga, H., Harrison, S.H., Barrick, J.E., 2015. Rapid evolution of silver nanoparticle resistance in Escherichia coli. Front. Genet. 6, 42. https://doi.org/10.3389/fgene.2015.00042.

Guo, C., Ding, P., Xie, C., Ye, C., Ye, M., Pan, C., Cao, X., Zhang, S., Zheng, S., 2017. Potential application of the oxidative nucleic acid damage biomarkers in detection of diseases. Oncotarget 8 (43), 75767–75777. https://doi.org/10.18632/oncotarget.20801.

Guo, Z., Liu, H., Wang, W., Hu, Z., Li, X., Chen, H., Wang, K., Li, Z., Yuan, C., Ge, X., 2024. Recent advances in antibacterial strategies based on TiO2 biomimetic micro/nano-structured surfaces fabricated using the hydrothermal method. Biomimetics 9 (11), 656. https://doi.org/10.3390/biomimetics9110656.

Gupta, A., Mumtaz, S., Li, C.H., Hussain, I., Rotello, V.M., 2019. Combatting antibiotic-resistant bacteria using nanomaterials. Chem. Soc. Rev. 48, 415–427. https://doi.org/10.1039/c7cs00748e.

Halim, J., Carr, R.A., Fliorent, R., Jonnalagadda, K., Kurbonnazarova, M., Kaur, M., Millstein, I., Carabetta, V.J., 2024. Combinations of antibiotics effective against Extensively- and pandrug-resistant Acinetobacter baumannii patient isolates. Microorganisms 12. https://doi.org/10.3390/microorganisms12071353.

Hamarawf, R.F., 2024. Antibacterial, antibiofilm, and antioxidant activities of two novel metal-organic frameworks (MOFs) based on 4,6-diamino-2-pyrimidinethiol with Zn and Co metal ions as coordination polymers. RSC Adv. 14, 9080–9098. https://doi.org/10.1039/d4ra00545g.

Hasan, N., Aftab, M., Ikram, S., Mustofa, A.Z., Sriwidodo, S., Darusman, H.S., Amir, M.N., Tockary, T.A., Uchida, S., 2026. Recent advances in lipid nanoparticles for cancer vaccine delivery: challenges and future perspectives. Int. J. Pharm. X 11, 100484. https://doi.org/10.1016/J.IJPX.2026.100484.

Hatami, M., Ghorbanpour, M., 2024. Metal and metal oxide nanoparticles-induced reactive oxygen species: phytotoxicity and detoxification mechanisms in plant cell. Plant Physiol. Biochem. 213, 108847. https://doi.org/10.1016/j.plaphy.2024.108847.

He, L., Yang, S., Xuan, W., Zhen, X., Qi, Q., Qi, Y., Li, Q., Du, M., Hamblin, M.R., Huang, L., 2023. Phenylalanine-Arginine-β-Naphthylamide enhances the photobactericidal effect of methylene blue on Pseudomonas aeruginosa. Photobiomodul. Photomed. Laser Surg. 41, 569–575. https://doi.org/10.1089/photob.2023.0005.

Hürkan, K., Hürkan, Y.K., 2024. Changes in plant gene expression in response to gold nanoparticles and gold ions. Smart Nanomater. Technol. https://doi.org/10.1007/978-981-97-7174-5_5.

Huang, Y., Guo, X., Wu, Y., Chen, X., Feng, L., Xie, N., Shen, G., 2024. Nanotechnology's frontier in combatting infectious and inflammatory diseases: prevention and treatment. Signal Transduct. Targeted Ther. 9 (1), 34. https://doi.org/10.1038/s41392-024-01745-z.

Hudecová, A., Kusznierewicz, B., Rundén-Pran, E., Magdolenová, Z., Hašplová, K., Rinna, A., Fjellsbo, L.M., Kruszewski, M., Lankoff, A., Sandberg, W.J., Refsnes, M., Skuland, T., Schwarze, P., Brunborg, G., Bjoras, M., Collins, A., Miadoková, E., Gálová, E., Dušinská, M., 2012. Silver nanoparticles induce premutagenic DNA oxidation that can be prevented by phytochemicals from Gentiana asclepiadea. Mutagenesis 27, 759–769. https://doi.org/10.1093/mutage/ges046.

Huma, Z., Gupta, A., Javed, I., Das, R., Hussain, S.Z., Mumtaz, S., Hussain, I., Rotello, V.M., 2018. Cationic silver nanoclusters as potent antimicrobials against multidrug-resistant bacteria. ACS Omega 3 (12), 16721–16727. https://doi.org/10.1021/acsomega.8b02438.

Hussain, M., Binici, B., O'Connor, L., Perrie, Y., 2024. Production of mRNA lipid nanoparticles using advanced crossflow micromixing. J. Pharm. Pharmacol. 76 (12), 1572–1583. https://doi.org/10.1093/jpp/rgae122.

Ibne Shoukani, H., Nisa, S., Bibi, Y., Ishfaq, A., Ali, A., Alharthi, S., Kubra, K.T., Zia, M., 2024. Green synthesis of polyethylene glycol coated, ciprofloxacin loaded CuO nanoparticles and its antibacterial activity against Staphylococcus aureus. Sci. Rep. 14, 21246. https://doi.org/10.1038/s41598-024-72322-1.

Iravani, S., Korbekandi, H., Mirmohammadi, S.V., Zolfaghari, B., 2014. Synthesis of silver nanoparticles: chemical, physical and biological methods. Res. Pharm. Sci. 9 (6), 385–406.

Islam, S., Ahmed, M.M.S., Islam, M.A., Hossain, N., Chowdhury, M.A., 2025. Advances in nanoparticles in targeted drug delivery–A review. Results Surf. Interfaces 19, 100529. https://doi.org/10.1016/J.RSURFI.2025.100529.

Jagtap, S., 2024. Two-component regulatory systems in microbial pathogenesis. Indust. Microbiol. Biotechnol. https://doi.org/10.1007/978-981-97-1912-9_13.

Javed, M.U., Hayat, M.T., Mukhtar, H., Imre, K., 2023. CRISPR-Cas9 system: a prospective pathway toward combatting antibiotic resistance. Antibiotics 12 (6), 1075. https://doi.org/10.3390/antibiotics12061075.

Jeevanandam, J., Barhoum, A., Chan, Y.S., Dufresne, A., Danquah, M.K., 2018. Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein J. Nanotechnol. 9, 1050–1074. https://doi.org/10.3762/BJNANO.9.98.

Jena, A.B., Samal, R.R., Bhol, N.K., Duttaroy, A.K., 2023. Cellular Red-Ox system in health and disease: the latest update. Biomed. Pharmacother. 162, 114606. https://doi.org/10.1016/J.BIOPHA.2023.114606.

Jennings, E., Thurston, T.L.M., Holden, D.W., 2017. Salmonella SPI-2 Type III secretion system effectors: molecular mechanisms and physiological consequences. Cell Host Microbe 22, 217–231. https://doi.org/10.1016/j.chom.2017.07.009.

Jia, B., Du, X., Wang, W., Qu, Y., Liu, X., Zhao, M., Li, W., Li, Y.-Q., 2022. Nanophysical antimicrobial strategies: a rational deployment of nanomaterials and physical stimulations in combating bacterial infections. Adv. Sci. (Weinh). 9, e2105252. https://doi.org/10.1002/advs.202105252.

Joseph, T.M., Kar Mahapatra, D., Esmaeili, A., Piszczyk, Ł., Hasanin, M.S., Kattali, M., Haponiuk, J., Thomas, S., 2023. Nanoparticles: taking a unique position in medicine. Nanomaterials (Basel) 13, 574. https://doi.org/10.3390/nano13030574.

Juodeikis, R., Carding, S.R., 2022. Outer membrane vesicles: biogenesis, functions, and issues. Microbiol. Mol. Biol. Rev. 86 (4), e00032. https://doi.org/10.1128/mmbr.00032-22, 22.

Jyakhwo, S., Dmitrenko, A., Vinogradov, V.V., 2025. Computer-aided discovery of synergistic drug-nanoparticle combinations for enhanced antimicrobial activity. ACS Appl. Mater. Interfaces 17, 11820–11830. https://doi.org/10.1021/acsami.4c21133.

Kamaly, N., Yameen, B., Wu, J., Farokhzad, O.C., 2016. Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. Chem. Rev. https://doi.org/10.1021/acs.chemrev.5b00346.

Kamat, S., Kumari, M., 2023. Emergence of microbial resistance against nanoparticles: mechanisms and strategies. Front. Microbiol. 14, 1102615. https://doi.org/10.3389/fmicb.2023.1102615.

Kang, M.S., Lee, S.Y., Kim, K.S., Han, D.W., 2020. State of the art biocompatible gold nanoparticles for cancer theragnosis. Pharmaceutics 12 (8), 701. https://doi.org/10.3390/pharmaceutics12080701.

Kapoor, D.U., Khanday, M.A., Pareek, A., Prajapati, B.G., 2025. Reengineering infection treatment: liposome-based innovations in antibacterial delivery. Results Chem. 16, 102417. https://doi.org/10.1016/J.RECHEM.2025.102417.

Kar, P., Muduli, S., Nayak, S., Nayak, R.K., Parhi, P.K., 2025. A comprehensive review on biogenic synthesis and environmental - applications of precious metal nanoparticles. J. Environ. Chem. Eng. 13, 119164. https://doi.org/10.1016/J.JECE.2025.119164.

Karnwal, A., Kumar, G., Pant, G., Hossain, K., Ahmad, A., Alshammari, M.B., 2023. Perspectives on usage of functional nanomaterials in antimicrobial therapy for antibiotic-resistant bacterial infections. ACS Omega 8, 13492–13508. https://doi.org/10.1021/acsomega.3c00110.

Kaya, M., Akdaşçi, E., Eker, F., Bechelany, M., Karav, S., 2025. Recent advances of silver nanoparticles in wound healing: evaluation of in vivo and in vitro studies. Int. J. Mol. Sci. https://doi.org/10.3390/ijms26209889.

Kaymaz, S.V., Nobar, H.M., Sarıgül, H., Soylukan, C., Akyüz, L., Yüce, M., 2023. Nanomaterial surface modification toolkit: principles, components, recipes, and applications. Adv. Colloid Interface Sci. 322, 103035. https://doi.org/10.1016/J.CIS.2023.103035.

Kędziora, A., Speruda, M., Wernecki, M., Dudek, B., Kapczyńska, K., Krzyżewska, E., Rybka, J., Bugla-Płoskońska, G., 2021. How bacteria change after exposure to silver nanoformulations: analysis of the genome and outer membrane proteome. Pathogens 10 (7), 817. https://doi.org/10.3390/pathogens10070817.

Keskin, D., Zu, G., Forson, A.M., Tromp, L., Sjollema, J., van Rijn, P., 2021. Nanogels: a novel approach in antimicrobial delivery systems and antimicrobial coatings. Bioact. Mater. https://doi.org/10.1016/j.bioactmat.2021.03.004.

Khairnar, S.V., Das, A., Oupický, D., Sadykov, M., Romanova, S., 2025. Strategies to overcome antibiotic resistance: silver nanoparticles and vancomycin in pathogen eradication. RSC Pharm. 2, 455–479. https://doi.org/10.1039/D4PM00314D.

Kheraldine, H., Rachid, O., Habib, A.M., Al Moustafa, A.E., Benter, I.F., Akhtar, S., 2021. Emerging innate biological properties of nano-drug delivery systems: a focus on PAMAM dendrimers and their clinical potential. Adv. Drug Deliv. Rev. 178, 113908. https://doi.org/10.1016/J.ADDR.2021.113908.

Kosikowska-Adamus, P., Golda, A., Ryl, J., Pilarczyk-Zurek, M., Bereta, G., Ossowski, T., Lesner, A., Koziel, J., Prahl, A., Niedziałkowski, P., 2024. Electrochemical detection of bacterial endotoxin lipopolysaccharide (LPS) on gold electrode modified with DAL-PEG-DK5-PEG-OH - Antimicrobial peptide conjugate. Talanta 273, 125881. https://doi.org/10.1016/j.talanta.2024.125881.

Krce, L., Šprung, M., Rončević, T.R., Maravić, A.M., Vedrana, V., Vedranačikeš, V., Vedrana čikeš Čulić, V., Blažeka, D., Krstulović, N.K., Aviani, I., 2020. Probing the mode of antibacterial action of silver nanoparticles synthesized by laser ablation in water: what fluorescence and AFM data tell us. Nanomaterials (Basel) 10 (6), 1040. https://doi.org/10.3390/nano10061040.

Kumar, M., Kulkarni, P., Liu, S., Chemuturi, N., Shah, D.K., 2023. Nanoparticle biodistribution coefficients: a quantitative approach for understanding the tissue distribution of nanoparticles. Adv. Drug Deliv. Rev. 194, 114708. https://doi.org/10.1016/j.addr.2023.114708.

Kumawat, M., Nabi, B., Daswani, M., Viquar, I., Pal, N., Sharma, P., Tiwari, S., Sarma, D. K., Shubham, S., Kumar, M., 2023. Role of bacterial efflux pump proteins in antibiotic resistance across microbial species. Microb. Pathog. 181, 106182. https://doi.org/10.1016/j.micpath.2023.106182.

Kurul, F., Turkmen, H., Cetin, A.E., Topkaya, S.N., 2025. Nanomedicine: how nanomaterials are transforming drug delivery, bio-imaging, and diagnosis. Next Nanotechnology 7, 100129. https://doi.org/10.1016/J.NXNANO.2024.100129.

Laib, I., Gheraissa, N., Benaissa, A., Benkhira, L., Azzi, M., Benaissa, Y., Abdelaziz, A.G., Tian, F., Walsh, M., Bechelany, M., Barhoum, A., 2025. Tailoring innovative silver nanoparticles for modern medicine: the importance of size and shape control and functional modifications. Mater. Today Bio 33, 102071. https://doi.org/10.1016/J.MTBIO.2025.102071.

Lalsangpuii, F., Rokhum, S.L., Nghakliana, F., Fakawmi, L., Ruatpuia, J.V.L., Laltlanmawii, E., Lalfakzuala, R., Siama, Z., 2022. Green synthesis of silver nanoparticles using spilanthes acmella leaf extract and its antioxidant-mediated ameliorative activity against doxorubicin-induced toxicity in dalton's lymphoma ascites (DLA)-bearing mice. ACS Omega 7, 44346–44359. https://doi.org/10.1021/ACSOMEGA.2C05970.

Lam, P.-L., Wong, R.S.-M., Lam, K.-H., Hung, L.-K., Wong, M.-M., Yung, L.-H., Ho, Y.-W., Wong, W.-Y., Hau, D.K.-P., Gambari, R., Chui, C.-H., 2020. The role of reactive oxygen species in the biological activity of antimicrobial agents: an updated mini review. Chem. Biol. Interact. 320, 109023. https://doi.org/10.1016/j.cbi.2020.109023.

Leanse, L.G., dos Anjos, C., Mushtaq, S., Dai, T., 2022. Antimicrobial blue light: a 'Magic Bullet' for the 21st century and beyond? Adv. Drug Deliv. Rev. 180, 114057. https://doi.org/10.1016/j.addr.2021.114057.

Li, H., Yang, Z., Khan, S.A., Walsh, L.J., Seneviratne, C.J., Ziora, Z.M., 2024. Characteristics of metallic nanoparticles (especially silver nanoparticles) as anti-biofilm agents. Antibiotics (Basel) 13, 819. https://doi.org/10.3390/antibiotics13090819.

Li, Q., Shen, X., Xing, D., 2023. Carbon quantum dots as ROS-Generator and -scavenger: a comprehensive review. Dyes Pigments 208, 110784. https://doi.org/10.1016/J.DYEPIG.2022.110784.

Li, X., Li, J., Wei, J., Du, W., Su, C., Shen, X., Zhao, A., Xu, M., 2025. Design strategies for novel lipid nanoparticle for mRNA vaccine and therapeutics: current understandings and future perspectives. MedComm 6. https://doi.org/10.1002/mco2.70414.

Liao, Y., Wang, X., Chen, P., Zhong, Q., Gong, J., 2025. Antimicrobial mechanisms of metal-based nanomaterials. Int. J. Nanomed. https://doi.org/10.2147/IJN.S557649.

Liu, M., Wang, L., Lo, Y., Shiu, S.C.C., Kinghorn, A.B., Tanner, J.A., 2022. Aptamer-enabled nanomaterials for therapeutics, drug targeting and imaging. Cells. https://doi.org/10.3390/cells11010159.

Liu, Y., Huang, Y., Kim, D., Ren, Z., Oh, M.J., Cormode, D.P., Hara, A.T., Zero, D.T., Koo, H., 2021. Ferumoxytol nanoparticles target biofilms causing tooth decay in the human mouth. Nano Lett. 21, 9442–9449. https://doi.org/10.1021/acs.nanolett.1c02702.

Liu, Y., Naha, P.C., Hwang, G., Kim, D., Huang, Y., Simon-Soro, A., Jung, H.I., Ren, Z., Li, Y., Gubara, S., Alawi, F., Zero, D., Hara, A.T., Cormode, D.P., Koo, H., 2018. Topical ferumoxytol nanoparticles disrupt biofilms and prevent tooth decay in vivo via intrinsic catalytic activity. Nat. Commun. 9. https://doi.org/10.1038/s41467-018-05342-x.

Liu, Y., Zhu, R., Liu, X., Li, D., Guo, M., Fei, B., Ren, Y., You, X., Li, Y., 2023. Effect of piperine on the inhibitory potential of MexAB-OprM efflux pump and imipenem resistance in carbapenem-resistant Pseudomonas aeruginosa. Microb. Pathog. 185, 106397. https://doi.org/10.1016/j.micpath.2023.106397.

Lu, X., Zhou, L., Song, W., 2024. Recent progress of electrospun nanofiber dressing in the promotion of wound healing. Polymers. https://doi.org/10.3390/polym16182596.

Lyagin, I., Aslanli, A., Domnin, M., Stepanov, N., Senko, O., Maslova, O., Efremenko, E., 2023. Metal nanomaterials and hydrolytic enzyme-based formulations for improved antifungal activity. Int. J. Mol. Sci. 24, 11359. https://doi.org/10.3390/ijms241411359.

Ma, X., Li, X., Luo, G., Jiao, J., 2022. DNA-functionalized gold nanoparticles: modification, characterization, and biomedical applications. Front. Chem. 10. https://doi.org/10.3389/fchem.2022.1095488.

Ma, X., Tian, Y., Yang, R., Wang, H., Allahou, L.W., Chang, J., Williams, G., Knowles, J. C., Poma, A., 2024. Nanotechnology in healthcare, and its safety and environmental risks. J. Nanobiotechnol. 22, 715. https://doi.org/10.1186/s12951-024-02901-x.

Maddiboyina, B., Roy, H., Ramaiah, M., Sarvesh, C.N., Hanuman Kosuru, S., Krishna Nakkala, R., Shankar Nayak, B., 2023. REVIEW open access Methicillin-resistant staphylococcus aureus: novel treatment approach breakthroughs. Bull. Natl. Res. Cent. 47, 95. https://doi.org/10.1186/s42269-023-01072-3.

Mahjoubian, M., Naeemi, A.S., Moradi-Shoeili, Z., Tyler, C.R., Mansouri, B., 2023. Oxidative stress, genotoxic effects, and other damages caused by chronic exposure to silver nanoparticles (Ag NPs) and zinc oxide nanoparticles (ZnO NPs), and their mixtures in zebrafish (Danio rerio). Toxicol. Appl. Pharmacol. 472, 116569. https://doi.org/10.1016/j.taap.2023.116569.

Makhlouf, Z., Ali, A.A., Al-Sayah, M.H., 2023. Liposomes-based drug delivery systems of anti-biofilm agents to combat bacterial biofilm formation. Antibiotics 12 (5), 875. https://doi.org/10.3390/antibiotics12050875.

Malik, S., Muhammad, K., Waheed, Y., 2023. Emerging applications of nanotechnology in healthcare and medicine. Molecules 28, 6624. https://doi.org/10.3390/molecules28186624.

Mammari, N., Lamouroux, E., Boudier, A., Duval, R.E., 2022. Current knowledge on the oxidative-stress-mediated antimicrobial properties of metal-based nanoparticles. Microorganisms 10 (2), 437. https://doi.org/10.3390/microorganisms10020437.

Manuja, A., Kumar, B., Kumar, R., Chhabra, D., Ghosh, M., Manuja, M., Brar, B., Pal, Y., Tripathi, B.N., Prasad, M., 2021. Metal/metal oxide nanoparticles: toxicity concerns associated with their physical state and remediation for biomedical applications. Toxicol. Rep. 8, 1970–1978. https://doi.org/10.1016/J.TOXREP.2021.11.020.

Marino, V., Sulmann, S., Koch, K.W., Dell'Orco, D., 2015. Structural effects of Mg2+ on the regulatory states of three neuronal calcium sensors operating in vertebrate phototransduction. Biochim. Biophys. Acta Mol. Cell Res. 1853, 2055–2065. https://doi.org/10.1016/J.BBAMCR.2014.10.026.

Marsala, V., Gerasymchuk, Y., Saladino, M.L., Paluch, E., Wawrzyńska, M., Boiko, V., Li, X., Giordano, C., Hreniak, D., Sobieszczańska, B., 2025. Structural, morphological, and antibacterial attributes of graphene oxide prepared by hummers'. Brodie's Methods. Molecules 30. https://doi.org/10.3390/molecules30020240.

Mayorga-Ramos, A., Zúñiga-Miranda, J., Carrera-Pacheco, S.E., Barba-Ostria, C., Guamán, L.P., 2023. CRISPR-Cas-based antimicrobials: design, challenges, and bacterial mechanisms of resistance. ACS Infect. Dis. 9, 1283–1302. https://doi.org/10.1021/acsinfecdis.2c00649.

Mba, I.E., Nweze, E.I., 2021. Nanoparticles as therapeutic options for treating multidrug-resistant bacteria: research progress, challenges, and prospects. World J. Microbiol. Biotechnol. https://doi.org/10.1007/s11274-021-03070-x.

McBee, M.E., Chionh, Y.H., Sharaf, M.L., Ho, P., Cai, M.W.L., Dedon, P.C., 2017. Production of superoxide in bacteria is stress- and cell state-dependent: a gating-optimized flow cytometry method that minimizes ROS measurement artifacts with fluorescent dyes. Front. Microbiol. 8. https://doi.org/10.3389/fmicb.2017.00459.

McBroom, A.J., Kuehn, M.J., 2007. Release of outer membrane vesicles by Gram-negative bacteria is a novel envelope stress response. Mol. Microbiol. 63 (2), 545–558. https://doi.org/10.1111/j.1365-2958.2006.05522.x.

Melese, A., Wubet, W., Abebe, A., Hussen, A., 2025. A comprehensive review on recent progress in synthesis methods of ZnO/CuO nanocomposites and their biological and photocatalytic applications. Results Chem. 14, 102141. https://doi.org/10.1016/J.RECHEM.2025.102141.

Michaelis, C., Grohmann, E., 2023. Horizontal gene transfer of antibiotic resistance genes in biofilms. Antibiotics (Basel) 12, 328. https://doi.org/10.3390/antibiotics12020328.

Modi, S.K., Gaur, S.G., Sengupta, M., Singh, M.S., 2023. Mechanistic insights into nanoparticle surface-bacterial membrane interactions in overcoming antibiotic resistance. Front. Microbiol. 14, 1135579. https://doi.org/10.3389/fmicb.2023.1135579.

Mohammed, A.M., Mohammed, M., Oleiwi, J.K., Ihmedee, F.H., Adam, T., Betar, B.O., Gopinath, S.C.B., 2025. Comprehensive review on zinc oxide nanoparticle production and the associated antibacterial mechanisms and therapeutic potential. Nano Trends 11, 100145. https://doi.org/10.1016/J.NWNANO.2025.100145.

Moradi, F., Ghaedi, A., Fooladfar, Z., Bazrgar, A., 2023. Recent advance on nanoparticles or nanomaterials with anti-multidrug resistant bacteria and anti-bacterial biofilm properties: a systematic review. Heliyon 9 (11), e22105. https://doi.org/10.1016/j.heliyon.2023.e22105.

More, P.R., Pandit, S., Filippis, A. De, Franci, G., Mijakovic, I., Galdiero, M., 2023. Silver nanoparticles: bactericidal and mechanistic approach against drug resistant pathogens. Microorganisms. https://doi.org/10.3390/microorganisms11020369.

Moreno, A., Sipponen, M.H., 2024. Overcoming challenges of lignin nanoparticles: expanding opportunities for scalable and multifunctional nanomaterials. Acc. Chem. Res. 57, 1918–1930. https://doi.org/10.1021/acs.accounts.4c00206.

Mota, C., Araújo, A.M., Enea, M., Pereira, E., Reis-Mendes, A., Fernandes, R., Pacheco, S., Lúcio, M., Martins Lopes, C., Ferreira, I.M.P.L.V.O., Carvalho, M., 2026. Are all nanoplastics equally neurotoxic? Influence of size and surface functionalization on the toxicity of polystyrene nanoplastics in human neuronal cells. Environ. Pollut. 390, 127445. https://doi.org/10.1016/J.ENVPOL.2025.127445.

Mourenza, Á., Gil, J.A., Mateos, L.M., Letek, M., 2020. Oxidative stress-generating antimicrobials, a novel strategy to overcome antibacterial resistance. Antioxidants 9 (5), 361. https://doi.org/10.3390/antiox9050361.

Munir, M.U., Ahmed, A., Usman, M., Salman, S., 2020. Recent advances in nanotechnology-aided materials in combating microbial resistance and functioning as antibiotics substitutes. Int. J. Nanomed. https://doi.org/10.2147/IJN.S265934.

Murray, C.J., Ikuta, K.S., Sharara, F., Swetschinski, L., Robles Aguilar, G., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., Johnson, S.C., Browne, A.J., Chipeta, M.G., Fell, F., Hackett, S., Haines-Woodhouse, G., Kashef Hamadani, B.H., Kumaran, E.A. P., McManigal, B., Agarwal, R., Akech, S., Albertson, S., Amuasi, J., Andrews, J., Aravkin, A., Ashley, E., Bailey, F., Baker, S., Basnyat, B., Bekker, A., Bender, R., Bethou, A., Bielicki, J., Boonkasidecha, S., Bukosia, J., Carvalheiro, C., Castañeda-Orjuela, C., Chansamouth, V., Chaurasia, S., Chiurchiù, S., Chowdhury, F., Cook, A. J., Cooper, B., Cressey, T.R., Criollo-Mora, E., Cunningham, M., Darboe, S., Day, N.P. J., De Luca, M., Dokova, K., Dramowski, A., Dunachie, S.J., Eckmanns, T., Eibach, D., Emami, A., Feasey, N., Fisher-Pearson, N., Forrest, K., Garrett, D., Gastmeier, P., Giref, A.Z., Greer, R.C., Gupta, V., Haller, S., Haselbeck, A., Hay, S.I., Holm, M., Hopkins, S., Iregbu, K.C., Jacobs, J., Jarovsky, D., Javanmardi, F., Khorana, M., Kissoon, N., Kobeissi, E., Kostyanev, T., Krapp, F., Krumkamp, R., Kumar, A., Kyu, H. H., Lim, C., Limmathurotsakul, D., Loftus, M.J., Lunn, M., Ma, J., Mturi, N., Munera-Huertas, T., Musicha, P., Mussi-Pinhata, M.M., Nakamura, T., Nanavati, R., Nangia, S., Newton, P., Ngoun, C., Novotney, A., Nwakanma, D., Obiero, C.W., Olivas-Martinez, A., Olliaro, P., Ooko, E., Ortiz-Brizuela, E., Peleg, A.Y., Perrone, C., Plakkal, N., Ponce-de-Leon, A., Raad, M., Ramdin, T., Riddell, A., Roberts, T., Robotham, J.V., Roca, A., Rudd, K.E., Russell, N., Schnall, J., Scott, J.A.G., Shivamallappa, M., Sifuentes-Osornio, J., Steenkeste, N., Stewardson, A.J., Stoeva, T., Tasak, N., Thaiprakong, A., Thwaites, G., Turner, C., Turner, P., van Doorn, H.R., Velaphi, S., Vongpradith, A., Vu, H., Walsh, T., Waner, S., Wangrangsimakul, T., Wozniak, T., Zheng, P., Sartorius, B., Lopez, A.D., Stergachis, A., Moore, C., Dolecek, C., Naghavi, M., 2022. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 399, 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0.

Muteeb, G., Kazi, R.N.A., Aatif, M., Azhar, A., Oirdi, M. El, Farhan, M., 2025. Antimicrobial resistance: linking molecular mechanisms to public health impact. SLAS Discovery 33, 100232. https://doi.org/10.1016/J.SLASD.2025.100232.

Muteeb, G., Rehman, M.T., Shahwan, M., Aatif, M., 2023. Origin of antibiotics and antibiotic resistance, and their impacts on drug development: a narrative review. Pharmaceuticals. https://doi.org/10.3390/ph16111615.

Nallanthighal, S., Chan, C., Murray, T.M., Mosier, A.P., Cady, N.C., Reliene, R., 2017. Differential effects of silver nanoparticles on DNA damage and DNA repair gene expression in Ogg1-deficient and wild type mice. Nanotoxicology 11, 996–1011. https://doi.org/10.1080/17435390.2017.1388863.

Nam, G., Rangasamy, S., Purushothaman, B., Song, J.M., 2015. The application of bactericidal silver nanoparticles in wound treatment. Nanomater. Nanotechnol. https://doi.org/10.5772/60918.

Nguyen, T.T.T., Nguyen, Y.N.N., Tran, X.T., Nguyen, Tam Thi Thanh, Tran, T. Van, 2023. Green synthesis of CuO, ZnO and CuO/ZnO nanoparticles using Annona glabra leaf extract for antioxidant, antibacterial and photocatalytic activities. J. Environ. Chem. Eng. 11, 111003. https://doi.org/10.1016/J.JECE.2023.111003.

Niedźwiadek, K., Polak-Berecka, M., Waśko, A., 2025. Innovations in biofilm prevention and eradication in medical sector: an integrative review. Pathogens. https://doi.org/10.3390/pathogens14121242.

Nwobodo, D.C., Ugwu, M.C., Anie, C.O., Al-Ouqaili, M.T.S., Ikem, J.C., Chigozie, U.V., Saki, M., 2022. Antibiotic resistance: the challenges and some emerging strategies for tackling a global menace. J. Clin. Lab. Anal. 36, e24655. https://doi.org/10.1002/jcla.24655.

Nyabadza, A., McCarthy, É., Makhesana, M., Heidarinassab, S., Plouze, A., Vazquez, M., Brabazon, D., 2023. A review of physical, chemical and biological synthesis methods of bimetallic nanoparticles and applications in sensing, water treatment, biomedicine, catalysis and hydrogen storage. Adv. Colloid Interface Sci. 321, 103010. https://doi.org/10.1016/J.CIS.2023.103010.

O'Keeffe, K.R., Carbone, I., Jones, C.D., Mitchell, C.E., 2017. Plastic potential: how the phenotypes and adaptations of pathogens are influenced by microbial interactions within plants. Curr. Opin. Plant Biol. 38, 78–83. https://doi.org/10.1016/j.pbi.2017.04.014.

Ogunsona, E.O., Muthuraj, R., Ojogbo, E., Valerio, O., Mekonnen, T.H., 2020. Engineered nanomaterials for antimicrobial applications: a review. Appl. Mater. Today 18, 100473. https://doi.org/10.1016/j.apmt.2019.100473.

Okeke, I.S., Agwu, K.K., Ubachukwu, A.A., Ezema, F.I., 2022. Influence of transition metal doping on physiochemical and antibacterial properties of ZnONanoparticles: a review. Appl. Surf. Sci. Adv. 8, 100227. https://doi.org/10.1016/J.APSADV.2022.100227.

Okkeh, M., Bloise, N., Restivo, E., De Vita, L., Pallavicini, P., Visai, L., 2021. Gold nanoparticles: can they be the next magic bullet for multidrug-resistant bacteria? Nanomaterials (Basel) 11 (2), 312. https://doi.org/10.3390/nano11020312.

Ommen, P., Hansen, L., Hansen, B.K., Vu-Quang, H., Kjems, J., Meyer, R.L., 2022. Aptamer-targeted drug delivery for Staphylococcus aureus biofilm. Front. Cell. Infect. Microbiol. 12. https://doi.org/10.3389/fcimb.2022.814340.

Osouli-Bostanabad, Karim, Sara Puliga, Serrano, Dolores R., Bucchi, Andrea, Halbert, Gavin, Lalatsa, Aikaterini, 2022. Microfluidic manufacture of lipid-based nanomedicines. Pharmaceutics 14 (9), 1940. https://doi.org/10.3390/pharmaceutics14091940.

P, R.B., Prajapati, B.G., Rajeshkumar, R., Balasubramaniam, V., Ponnusankar, S., 2025. Revolutionizing antibacterial strategies: lipid nanoparticles as game-changers in combatting multi-drug-resistant infections. Curr. Med. Chem. 32 (8), 1488–1506. https://doi.org/10.2174/0109298673314366240712105637.

Pachghare, P., Zambre, D., Malode, D., Kale, M., Wankhede, N., Trivedi, R., Umekar, M., Raut, N., 2025. Combating multi-drug resistance with silver nanoparticles: a systematic review. Microbe 9, 100608. https://doi.org/10.1016/J.MICROB.2025.100608.

Pal, S., Tak, Y.K., Song, J.M., 2007. Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the Gram-negative bacterium Escherichia coli. Appl. Environ. Microbiol. 73 (6), 1712–1720. https://doi.org/10.1128/AEM.02218-06.

Pancu, D.F., Scurtu, A., Macasoi, I.G., Marti, D., Mioc, M., Soica, C., Coricovac, D., Horhat, D., Poenaru, M., Dehelean, C., 2021. Antibiotics: conventional therapy and natural compounds with antibacterial activity-a pharmaco-toxicological screening. Antibiotics 10. https://doi.org/10.3390/antibiotics10040401.

Pang, Z., Raudonis, R., Glick, B.R., Lin, T.J., Cheng, Z., 2019. Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies. Biotechnol. Adv. 37, 177–192. https://doi.org/10.1016/J.BIOTECHADV.2018.11.013.

Pechnikova, N.A., Poimenidou, M., Patsidou, C., Zafeiriou-Chatziefraimidou, M., Iliadis, I., Yaremenko, A.V., 2025. Engineered nanoparticles for combating drug-resistant bacteria and bacterial biofilms. ACS Nano Med. https://doi.org/10.1021/acsnanomed.5c00060.

Piattelli, E., Peltier, J., Soutourina, O., 2020. Interplay between regulatory RNAs and signal transduction systems during bacterial infection. Genes 11, 1209. https://doi.org/10.3390/genes11101209.

Pinto, R.M., Soares, F.A., Reis, S., Nunes, C., Van Dijck, P., 2020. Innovative strategies toward the disassembly of the EPS matrix in bacterial biofilms. Front. Microbiol. 11, 952. https://doi.org/10.3389/fmicb.2020.00952.

Politano, A.D., Campbell, K.T., Rosenberger, L.H., Sawyer, R.G., 2013. Use of silver in the prevention and treatment of infections: silver review. Surg. Infect. (Larchmt). https://doi.org/10.1089/sur.2011.097.

Priya, S., Malviya, R., Srivastava, S., Siang, T.C., Aseeri, A.A., 2026. Bioinspired nanostructured surfaces for antimicrobial and antifouling applications. Colloid Interface Sci. Commun. 70, 100863. https://doi.org/10.1016/J.COLCOM.2025.100863.

Provoda, C.J., Lee, K.D., 2000. Bacterial pore-forming hemolysins and their use in the cytosolic delivery of macromolecules. Adv. Drug Deliv. Rev. 41, 209–221. https://doi.org/10.1016/S0169-409X(99)00067-8.

Qiang, S., Zhang, L., Li, Z., Liang, J., Li, P., Song, J., Guo, K., Wang, Z., Fan, Q., 2022. New insights into the cellular toxicity of carbon quantum dots to Escherichia coli. Antioxidants 11. https://doi.org/10.3390/antiox11122475.

Ramamurthy, R., Mehta, C.H., Nayak, U.Y., 2021. Structurally nanoengineered antimicrobial peptide polymers: design, synthesis and biomedical applications. World J. Microbiol. Biotechnol. https://doi.org/10.1007/s11274-021-03109-z.

Rana, S., Kumar, A., Wang, T., Dhiman, P., Sharma, G., 2024. Recent progress and new insights on semiconductor heterojunctions powered photocatalytic desulphurization: a review. Chemosphere 364, 143237. https://doi.org/10.1016/J.CHEMOSPHERE.2024.143237.

Rashid, M.H., Sujoy, S.I., Rahman, M.S., Haque, M.J., 2024. Aloe vera assisted green synthesis of Ag and Cu co-doped ZnO nanoparticles and a comprehensive analysis of their structural, morphological, optical, electrical and antibacterial properties. Heliyon 10, e25438. https://doi.org/10.1016/J.HELIYON.2024.E25438.

Regulski, M., Myntti, M.F., James, G.A., 2023. Anti-biofilm efficacy of commonly used wound care products in in vitro settings. Antibiotics 12 (3), 536. https://doi.org/10.3390/antibiotics12030536.

Rodríguez-Gómez, F.D., Monferrer, D., Penon, O., Rivera-Gil, P., 2025. Regulatory pathways and guidelines for nanotechnology-enabled health products: a comparative review of EU and US frameworks. Front. Med. 12, 1544393. https://doi.org/10.3389/fmed.2025.1544393.

Rodrigues, A.S., Batista, J.G.S., Rodrigues, M.Á.V., Thipe, V.C., Minarini, L.A.R., Lopes, P.S., Lugão, A.B., 2024. Advances in silver nanoparticles: a comprehensive review on their potential as antimicrobial agents and their mechanisms of action elucidated by proteomics. Front. Microbiol. 15, 1440065. https://doi.org/10.3389/fmicb.2024.1440065.

Rukholm, G., Mugabe, C., Azghani, A.O., Omri, A., 2006. Antibacterial activity of liposomal gentamicin against Pseudomonas aeruginosa: a time–kill study. Int. J. Antimicrob. Agents 27, 247–252. https://doi.org/10.1016/J.IJANTIMICAG.2005.10.021.

Sadoon, A.A., Khadka, P., Freeland, J., Gundampati, R.K., Manso, R.H., Ruiz, M., Krishnamurthi, V.R., Thallapuranam, S.K., Chen, J., Wang, Y., 2020. Silver ions caused faster diffusive dynamics of histone-like nucleoid-structuring proteins in live bacteria. Appl. Environ. Microbiol. 86 (6), e02479. https://doi.org/10.1128/AEM.02479-19, 19.

Sa'ed, M.M., Ayivi, R.D., Wei, J., Obare, S.O., 2024. Gold nanoparticles antibacterial activity: does the surface matter? Colloid Interface Sci. Commun. 62, 100804. https://doi.org/10.1016/J.COLCOM.2024.100804.

Sahli, C., Moya, S.E., Lomas, J.S., Gravier-Pelletier, C., Briandet, R., Hémadi, M., 2022. Recent advances in nanotechnology for eradicating bacterial biofilm. Theranostics 12, 2383–2405. https://doi.org/10.7150/thno.67296.

Salam, M.A., Al-Amin, M.Y., Salam, M.T., Pawar, J.S., Akhter, N., Rabaan, A.A., Alqumber, M.A.A., 2023. Antimicrobial resistance: a growing serious threat for global public health. Healthcare 11, 1946. https://doi.org/10.3390/healthcare11131946.

Saleemi, M.A., Kong, Y.L., Yong, P.V.C., Wong, E.H., 2022. An overview of antimicrobial properties of carbon nanotubes-based nanocomposites. Adv. Pharmaceut. Bull. https://doi.org/10.34172/apb.2022.049.

Saleh, M.M., Sadeq, R.A., Abdel Latif, H.K., Abbas, H.A., Askoura, M., 2019. Zinc oxide nanoparticles inhibits quorum sensing and virulence in Pseudomonas aeruginosa. Afr. Health Sci. 19 (2), 2043–2055. https://doi.org/10.4314/ahs.v19i2.28.

Sati, A., Ranade, T.N., Mali, S.N., Ahmad Yasin, H.K., Pratap, A., 2025. Silver nanoparticles (AgNPs): comprehensive insights into bio/synthesis, key influencing factors, multifaceted applications, and toxicity—a 2024 Update. ACS Omega 10 (8), 7549–7582. https://doi.org/10.1021/acsomega.4c11045.

Scott, M.B., Styring, A.K., McCullagh, J.S.O., 2022. Polyphenols: bioavailability, microbiome interactions and cellular effects on health in humans and animals. Pathogens 11, 770. https://doi.org/10.3390/pathogens11070770.

Sedighi, O., Bednarke, B., Sherriff, H., Doiron, A.L., 2024. Nanoparticle-based strategies for managing biofilm infections in wounds: a comprehensive review. ACS Omega 9, 27853–27871. https://doi.org/10.1021/acsomega.4c02343.

Shah, R.M., Kaur, I.P., Jadhav, S.R., 2026. The surface-first paradigm: engineering nanocarriers for infection-responsive drug delivery. Adv. Colloid Interface Sci. 349, 103761. https://doi.org/10.1016/J.CIS.2025.103761.

Sharma, S., Kaushik, V., Kulshrestha, M., Tiwari, V., 2023. Different efflux pump systems in Acinetobacter baumannii and their role in multidrug resistance. Adv. Exp. Med. Biol. https://doi.org/10.1007/5584_2023_771.

Shirley, M., 2019. Amikacin liposome inhalation suspension: a review in Mycobacterium avium complex lung disease. Drugs 79 (5), 555–562. https://doi.org/10.1007/s40265-019-01095-4.

Shrestha, S., Wang, B., Dutta, P.K., 2024. Commercial silver-based dressings: in vitro and clinical studies in treatment of chronic and burn wounds. Antibiotics 13 (9), 910. https://doi.org/10.3390/antibiotics13090910.

Shukla, B.K., Sharma, P.K., Yadav, H., Singh, S., Tyagi, K., Yadav, Y., Rajpoot, N.K., Rawat, S., Verma, S., 2024. Advanced membrane technologies for water treatment: utilization of nanomaterials and nanoparticles in membranes fabrication. J. Nanoparticle Res. 26. https://doi.org/10.1007/s11051-024-06117-w.

Singh, R., Rawat, H., Kumar, A., Gandhi, Y., Kumar, V., Mishra, S.K., Narasimhaji, C.V., 2024. Graphene and its hybrid nanocomposite: a metamorphoses elevation in the field of tissue engineering. Heliyon 10, e33542. https://doi.org/10.1016/J.HELIYON.2024.E33542.

Sohail, A., 2025. Progress in nanomaterials: synthesis, characterization, and applications. Next Nanotechnology 8, 100263. https://doi.org/10.1016/J.NXNANO.2025.100263.

Solanki, R., Makwana, N., Kumar, R., Joshi, M., Patel, A., Bhatia, D., Sahoo, D.K., 2024. Nanomedicines as a cutting-edge solution to combat antimicrobial resistance. RSC Adv. 14, 33568–33586. https://doi.org/10.1039/D4RA06117A.

Sondi, I., Salopek-Sondi, B., 2004. Silver nanoparticles as antimicrobial agent: a case study on E. coli as a model for Gram-negative bacteria. J. Colloid Interface Sci. 275, 177–182. https://doi.org/10.1016/J.JCIS.2004.02.012.

Staats, G.J., 2022. Evaluating the Role of Efflux Pumps in Bacterial Disinfectant Resistance. University of the Free State. Doctoral dissertation.

Su, L.J., Zhang, J.H., Gomez, H., Murugan, R., Hong, X., Xu, D., Jiang, F., Peng, Z.Y., 2019. Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis. Oxid. Med. Cell. Longev. https://doi.org/10.1155/2019/5080843.

Summer, M., Ashraf, R., Ali, S., Bach, H., Noor, S., Noor, Q., Riaz, S., Khan, R.R.M., 2024. Inflammatory response of nanoparticles: mechanisms, consequences, and strategies for mitigation. Chemosphere 363, 142826. https://doi.org/10.1016/j.chemosphere.2024.142826.

Sun, L., Li, M., Yang, J., Li, J., 2022. Cell membrane-coated nanoparticles for management of infectious diseases: a review. Ind. Eng. Chem. Res. 61, 12867–12883. https://doi.org/10.1021/acs.iecr.2c01587.

Syed, S.M., Kulkarni, S., Patil, M., Satpute, K., 2026. A comprehensive review of green synthesis methods and applications of nanoparticles derived from plant extracts and microorganisms. Discov. Green Chem. 1, 6. https://doi.org/10.1007/s44509-026-00006-2.

TabibzadehTehrani, P., Nazari, M., Rastgoo, P., Bolouri, N.S., HeydariKarsaf, R., Hadiani, A., Mohsenipour, Z., 2025. Bacterial-based drug delivery systems: a new way to combat infectious disease. Med. Drug Discov. 26, 100205. https://doi.org/10.1016/J.MEDIDD.2025.100205.

Tabrizi, E., Li, B., 2025. Silver integrated hybrids and nanocomposites for next-generation biomedicine: beyond antimicrobial coatings toward smart sense–response–heal platforms. Mater. Today Bio 35, 102609. https://doi.org/10.1016/J.MTBIO.2025.102609.

Taha, B.A., Addie, A.J., Chahal, S., Haider, A.J., Rustagi, S., Arsad, N., Chaudhary, V., 2025. Unlocking new frontiers in healthcare: the impact of nano-optical biosensors on personalized medical diagnostics. J. Biotechnol. 400, 29–47. https://doi.org/10.1016/J.JBIOTEC.2025.02.005.

Takallu, S., Aiyelabegan, H.T., Zomorodi, A.R., Alexandrovna, K.V., Aflakian, F., Asvar, Z., Moradi, F., Behbahani, M.R., Mirzaei, E., Sarhadi, F., Vakili-Ghartavol, R., 2024. Nanotechnology improves the detection of bacteria: recent advances and future perspectives. Heliyon 10, e32020. https://doi.org/10.1016/J.HELIYON.2024.E32020.

Tan, Y., Cao, Y., Mou, F., Liu, B., Wu, H., Zou, S., Ai, L., Sui, S., 2024. Transcriptome profiling of two Camellia japonica cultivars with different heat tolerance reveals heat stress response mechanisms. Plants (Basel) 13, 3089. https://doi.org/10.3390/plants13213089.

Tavan, M., Yousefian, Z., Bakhtiar, Z., Rahmandoust, M., Mirjalili, M.H., 2025. Carbon quantum dots: multifunctional fluorescent nanomaterials for sustainable advances in biomedicine and agriculture. Ind. Crops Prod. 231, 121207. https://doi.org/10.1016/J.INDCROP.2025.121207.

Teixeira-Santos, R., Gomes, M., Gomes, L.C., Mergulhã, F.J., 2021. iScience antimicrobial and anti-adhesive properties of carbon nanotube-based surfaces for medical applications: a systematic review. Science 24, 102001. https://doi.org/10.1016/j.isci.

Thakur, A., Ganesan, R., Ray Dutta, J., 2026. Nanomaterials against antimicrobial resistance and beyond: toward mitigating bacterial resuscitation. Total Environ. Microbiol. 2, 100052. https://doi.org/10.1016/J.TEMICR.2025.100052.

Ullah, K., Yan, H., Shao, Y., Zhang, Hui, Zhang, Haiping, Zhu, J., 2026. A review on innovations in antimicrobial nanotechnology: integrating silver nanoparticles and carbon nanomaterials. Particuology 114, 164–185. https://doi.org/10.1016/J.PARTIC.2026.04.004.

Uneputty, A., Dávila-Lezama, A., Garibo, D., Oknianska, A., Bogdanchikova, N., Hernández-Sánchez, J.F., Susarrey-Arce, A., 2022. Strategies applied to modify structured and smooth surfaces: a step closer to reduce bacterial adhesion and biofilm formation. Colloid Interface Sci. Commun. 46, 100560. https://doi.org/10.1016/J.COLCOM.2021.100560.

Uprety, B., Abrahamse, H., 2022. Semiconductor quantum dots for photodynamic therapy: recent advances. Front. Chem. https://doi.org/10.3389/fchem.2022.946574.

Ural, M.S., Menéndez-Miranda, M., Salzano, G., Mathurin, J., Aybeke, E.N., Deniset-Besseau, A., Dazzi, A., Porcino, M., Martineau-Corcos, C., Gref, R., 2021. Compartmentalized polymeric nanoparticles deliver vancomycin in a pH-responsive manner. Pharmaceutics 13. https://doi.org/10.3390/pharmaceutics13121992.

Vaishampayan, A., Grohmann, E., 2022. Antimicrobials functioning through ROS-mediated mechanisms: current insights. Microorganisms 10 (1), 61. https://doi.org/10.3390/microorganisms10010061.

Van Aken, B., 2015. Gene expression changes in plants and microorganisms exposed to nanomaterials. Curr. Opin. Biotechnol. 33, 206–219. https://doi.org/10.1016/j.copbio.2015.03.005.

Vanlalveni, C., Ralte, V., Zohmingliana, H., Das, S., Anal, J.M.H., Lallianrawna, S., Rokhum, S.L., 2024. A review of microbes mediated biosynthesis of silver nanoparticles and their enhanced antimicrobial activities. Heliyon 10, e32333. https://doi.org/10.1016/J.HELIYON.2024.E32333.

Varaprasad, K., 2023. Antimicrobial Activity of Titanium Dioxide, Zinc Oxide and Copper Oxide Nanoparticles. Doctoral Dissertation. Goa University.

Vignesh, J., Ramesh, B., Xavier, J.R., 2026. Recent advances in multifunctional nanocomposites for high-performance and durable concrete in harsh environments. Results Eng. 29, 108840. https://doi.org/10.1016/J.RINENG.2025.108840.

Wahab, S., Khan, T., Adil, M., Khan, A., 2021. Mechanistic aspects of plant-based silver nanoparticles against multi-drug resistant bacteria. Heliyon 7, e07448. https://doi.org/10.1016/J.HELIYON.2021.E07448.

Wang, L., Wei, X., Liu, H., Fan, Y., 2023. Nanomaterial-mediated photoporation for intracellular delivery. Acta Biomater. 157, 24–48. https://doi.org/10.1016/j.actbio.2022.12.050.

Wang, Q., Wang, L., Liu, X., Chen, H., Wang, X., Wang, P., Wang, W., Jiang, Q., 2025. A pH-responsive magnetic-controlled Nanocomposite for Precise and Efficient

Vancomycin Delivery in Treating Prosthetic Joint Infections, 8, p. 115. https://doi.org/10.1007/s42114-024-01079-y.
Wang, Y., Ding, X., Chen, Y., Guo, M., Zhang, Y., Guo, X., Gu, H., 2016. Antibiotic-loaded, silver core-embedded mesoporous silica nanovehicles as a synergistic antibacterial agent for the treatment of drug-resistant infections. Biomaterials 101, 207–216. https://doi.org/10.1016/J.BIOMATERIALS.2016.06.004.
Wang, Z., Changotra, R., Dasog, M., Singh Selopal, G., Yang, J., He, Q.S., 2025. Carbon quantum dots: synthesis via hydrothermal processing, doping strategies, integration with photocatalysts, and their application in photocatalytic hydrogen production. Sustain. Mater. Technol. 44, e01386. https://doi.org/10.1016/J.SUSMAT.2025.E01386.
Waqas, U., Farhan, A., Haider, A., Qumar, U., Raza, A., 2023. Advancements in biofilm formation and control in potable water distribution systems: a comprehensive review and analysis of chloramine decay in water systems. J. Environ. Chem. Eng. 11, 111377. https://doi.org/10.1016/J.JECE.2023.111377.
Wu, J., Li, F., Hu, X., Lu, J., Sun, X., Gao, J., Ling, D., 2019. Responsive assembly of silver nanoclusters with a biofilm locally amplified bactericidal effect to enhance treatments against multi-drug-resistant bacterial infections. ACS Cent. Sci. 5, 1366–1376. https://doi.org/10.1021/acscentsci.9b00359.
Wu, J., Zhu, Z., Liu, W., Zhang, Y., Kang, Y., Liu, J., Hu, C., Wang, R., Zhang, M., Chen, L., Shao, L., 2022. How nanoparticles open the paracellular route of biological barriers: mechanisms, applications, and prospects. ACS Nano 16, 15627–15652. https://doi.org/10.1021/acsnano.2c05317.
Wu, K., Li, H., Cui, X., Feng, R., Chen, W., Jiang, Y., Tang, C., Wang, Y., Wang, Y., Shen, X., Liu, Y., Lynch, M., Long, H., 2022. Mutagenesis and resistance development of bacteria challenged by silver nanoparticles. Antimicrob. Agents Chemother. 66, e00628. https://doi.org/10.1128/aac.00628-22, 22.
Wu, K., Yang, Y., Zhang, Y., Deng, J., Lin, C., 2015. Antimicrobial activity and cytocompatibility of silver nanoparticles coated catheters via a biomimetic surface functionalization strategy. Int. J. Nanomed. 10, 7241–7252. https://doi.org/10.2147/IJN.S92307.
Xiao, J., Gao, X., Xu, J., Tan, J., Zhang, X., Zhang, H., 2025. Unveiling the synergistic effects in graphene-based composites as a new strategy for high performance and sustainable material development: a critical review. Sustainability (Switzerland). https://doi.org/10.3390/su172210058.
Xiao, W., Jiang, W., Chen, Z., Huang, Y., Mao, J., Zheng, W., Hu, Y., Shi, J., 2025. Advance in peptide-based drug development: delivery platforms, therapeutics and vaccines. Signal Transduct. Targeted Ther. https://doi.org/10.1038/s41392-024-02107-5.
Xu, M., Yang, Q., Xu, L., Rao, Z., Cao, D., Gao, M., Liu, S., 2019. Protein target identification and toxicological mechanism investigation of silver nanoparticles-induced hepatotoxicity by integrating proteomic and metallomic strategies. Part. Fibre Toxicol. 16. https://doi.org/10.1186/s12989-019-0322-4.
Xu, Z., Wu, Y., Hu, J., Mei, Z., Zhao, Y., Yang, K., Shi, Y., Xu, X., 2024. Recent advances in nanoadjuvant-triggered STING activation for enhanced cancer immunotherapy. Heliyon 10, e38900. https://doi.org/10.1016/J.HELIYON.2024.E38900.
Yadav, N., Sharma, A., Yano, Taka-aki Yano, Anthopoulos, T.D., Mishra, V., 2026. Next-generation functionalized carbon quantum dots: synthesis approach, structure, photoluminescence mechanism, and multifunctional applications. Coord. Chem. Rev. 548, 217152. https://doi.org/10.1016/J.CCR.2025.217152.
Yamasaki, S., Zwama, M., Yoneda, T., Hayashi-Nishino, M., Nishino, K., 2023. Drug resistance and physiological roles of RND multidrug efflux pumps in Salmonella enterica, Escherichia coli and Pseudomonas aeruginosa. Microbiology (Read.) 169, 1322. https://doi.org/10.1099/mic.0.001322.
Yan, X., He, B., Liu, L., Qu, G., Shi, J., Hu, L., Jiang, G., 2018. Antibacterial mechanism of silver nanoparticles in Pseudomonas aeruginosa: proteomics approach. Metallomics 10 (4), 557–564. https://doi.org/10.1039/C7MT00328E.
Yang, H., Zhang, J., Li, Z., Huang, J., Wu, J., Zhang, Y., Ge, H., Zhao, Y., 2023. Antibacterial effect of low-concentration ZnO nanoparticles on sulfate-reducing bacteria under visible light. Nanomaterials 13 (14), 2033. https://doi.org/10.3390/nano13142033.
Yetisgin, A.A., Cetinel, S., Zuvin, M., Kosar, A., Kutlu, O., 2020. Therapeutic nanoparticles and their targeted delivery applications. Molecules 25 (9), 2193. https://doi.org/10.3390/molecules25092193.
Ying, S., Guan, Z., Ofoegbu, P.C., Clubb, P., Rico, C., He, F., Hong, J., 2022. Green synthesis of nanoparticles: current developments and limitations. Environ. Technol. Innov. 26, 102336. https://doi.org/10.1016/J.ETI.2022.102336.
Yousefian, F., Hesari, R., Jensen, T., Obagi, S., Rgeai, A., Damiani, G., Bunick, C.G., Grada, A., 2023. Antimicrobial wound dressings: a concise review for Clinicians. Antibiotics 12 (9), 1434. https://doi.org/10.3390/antibiotics12091434.
Yusuf, A., Almotairy, A.R.Z., Henidi, H., Alshehri, O.Y., Aldughaim, M.S., 2023. Nanoparticles as drug delivery systems: a review of the implication of nanoparticles' physicochemical properties on responses in biological systems. Polymers. https://doi.org/10.3390/polym15071596.
Zaki, N.F., Orabi, S.H., Abdel-Bar, H.M., Korany, R.M., AlShuraym, L.A., Alkeridis, L.A., Ahmed, M.M., 2025. Zinc oxide resveratrol nanoparticles ameliorate levofloxacin-induced hepatotoxicity in rat model. BMC Pharmacol. Toxicol. 26. https://doi.org/10.1186/s40360-025-01068-x.
Zang, W., Cao, H., Ge, J., Zhao, D., 2024. Structures, physical properties and antibacterial activity of silver nanoparticles of Lactiplantibacillus plantarum exopolysaccharide. Int. J. Biol. Macromol. 263, 130083. https://doi.org/10.1016/j.ijbiomac.2024.130083.
Zeng, S., Chen, Y., Zhou, F., Zhang, T., Fan, X., Chrzanowski, W., Gillies, M.C., Zhu, L., 2023. Recent advances and prospects for lipid-based nanoparticles as drug carriers in the treatment of human retinal diseases. Adv. Drug Deliv. Rev. 199, 114965. https://doi.org/10.1016/J.ADDR.2023.114965.
Zhang, C., Wang, J., Chi, R., Shi, J., Yang, Y., Zhang, X., 2019. Reduced graphene oxide loaded with MoS2 and Ag3PO4 nanoparticles/PVA interpenetrating hydrogels for improved mechanical and antibacterial properties. Mater. Des. 183, 108166. https://doi.org/10.1016/J.MATDES.2019.108166.
Zhang, G., Fang, H., Chang, S., Chen, R., Li, L., Wang, D., Liu, Y., Sun, R., Zhao, Y., Li, B., 2023. Fullerene [60] encapsulated water-soluble supramolecular cage for prevention of oxidative stress-induced myocardial injury. Mater. Today Bio 21, 100693. https://doi.org/10.1016/J.MTBIO.2023.100693.
Zhang, L., Ouyang, S., Zhang, H., Qiu, M., Dai, Y., Wang, S., Wang, Y., Ou, J., 2021. Graphene oxide induces dose dependent lung injury in rats by regulating autophagy. Exp. Ther. Med. 21. https://doi.org/10.3892/etm.2021.9893.
Zhang, Q., Wang, R., Wang, M., Liu, C., Koohi-Moghadam, M., Wang, H., Ho, P.-L., Li, H., Sun, H., 2022. Re-sensitization of mcr carrying multidrug resistant bacteria to colistin by silver. Proc. Natl. Acad. Sci. U. S. A 119 (11), e2119417119. https://doi.org/10.1073/pnas.2119417119.
Zhang, X., Peng, F., Wang, D., 2022. MOFs and MOF-derived materials for antibacterial application. J. Funct. Biomater. https://doi.org/10.3390/jfb13040215.
Zhang, Z., Chen, Y., Gao, J., Yang, M., Zhang, D., Wang, L., Zhang, T., Cao, Q., Mwangi, J., He, C., Li, Y., Liu, X., Jiang, X., Kamau, P.M., Lai, R., 2023. Orientational nanoconjugation with gold endows marked antimicrobial potential and drugability of ultrashort dipeptides. Nano Lett. 23, 11874–11883. https://doi.org/10.1021/acs.nanolett.3c03909.
Ziental, D., Czarczynska-Goslinska, B., Mlynarczyk, D.T., Glowacka-Sobotta, A., Stanisz, B., Goslinski, T., Sobotta, L., 2020. Titanium dioxide nanoparticles: prospects and applications in medicine. Nanomaterials (Basel) 10, 387. https://doi.org/10.3390/nano10020387.
Zuo, L., Ren, K., Guo, X., Pokhrel, P., Pokhrel, B., Hossain, M.A., Chen, Z.X., Mao, H., Shen, H., 2023. Amalgamation of DNAzymes and nanozymes in a coronazyme. J. Am. Chem. Soc. 145 (10), 5750–5758. https://doi.org/10.1021/jacs.2c12367.