SHIFTING FROM TRADITIONAL ANTIBIOTICS TO NANOPARTICLE-BASED THERAPEUTICS AS PROMISING ALTERNATIVES AGAINST MULTI-DRUG-RESISTANT PATHOGENS

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Infectious diseases and biofilm-associated infections represent significant clinical challenges due to antimicrobial resistance (AMR), poor drug bioavailability, and limited penetration into infection sites. Nanoparticle-based systems offer innovative strategies to overcome these limitations by enabling targeted delivery, controlled release, and enhanced antimicrobial efficacy. Recent progress demonstrates their ability to disrupt biofilms, improve drug pharmacokinetics, and be functionalized for pathogen-specific activity. By consolidating these advances and examining their translational potential, this work emphasizes nanoparticle therapeutics as practical and adaptable alternatives to conventional antibiotics, while also identifying key obstacles and future directions for their clinical implementation.

Keywords: nanotechnology; antimicrobial nanoparticles; antibiofilm activity; alternatives to antibiotics; drug delivery;

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1. Introduction

Despite advances in the pharmaceutical domain, infectious diseases remain a leading cause of global morbidity and mortality, with biofilms presenting a particularly challenging issue in clinical facilities [1,2]. Pathogenic microorganisms (e.g., bacteria, fungi, viruses, protozoa, and even algae) are omnipresent in both environmental and hospital settings. Their persistence, coupled with growing drug resistance and increasing biofilm-associated complications, underscores an urgent need for alternative therapeutic strategies [1,3].

Biofilms are aggregated microorganism communities surrounded by self-produced extracellular polymeric substances (EPS), which confer high resistance to antimicrobial agents and immune responses [4-6]. These sessile microbial communities typically settle on implanted medical devices (e.g., catheters, prosthetics, heart valves, and pacemakers), acting as reservoirs for chronic and relapsing infections [7-11]. The EPS barrier, metabolic heterogeneity, quorum sensing, and efflux activity together protect embedded pathogens [12,13], often rendering conventional treatment approaches ineffective and necessitating the surgical removal of the infected device, prolonged hospital stays, increased healthcare costs, and substantial patient morbidity [7,14].

Beyond biofilm-associated complications, the continued emergence of multidrug-resistant (MDR) pathogens further exacerbates the complexity of infection management. Although conventional antibiotics have revolutionized modern medicine, their effectiveness is increasingly compromised by pharmacokinetic limitations such as poor solubility, rapid systemic clearance, inadequate penetration into infected tissues, and dose-limiting toxicity [15-17]. Moreover, indiscriminate use of antimicrobials has accelerated the evolution of resistance mechanisms, further reducing therapeutic options [16]. In these circumstances, nanotechnology appeared as a transformative approach in the fight against infectious diseases. Nanoparticles (NPs) exhibit unique physicochemical characteristics, including ultrasmall dimensions, high surface area-to-volume ratios, and tunable surface functionalities, making them highly efficient carriers for antimicrobial agents [18-21]. Inorganic NPs, like silver-, zinc oxide-, and iron oxide-based nanomaterials, display intrinsic antimicrobial activity, operating through multifaceted mechanisms that reduce the likelihood of resistance development [9,22,23].

NPs can also penetrate biofilms more efficiently than conventional antimicrobials and can be functionalized with specific ligands to target bacterial cells actively, enhancing therapeutic selectivity and minimizing systemic toxicity [24,25]. Furthermore, integrating stimuli-responsive mechanisms enables spatiotemporally controlled drug delivery to the infection site, improving efficacy while reducing off-target effects [16]. Recent efforts have also focused on

incorporating nanomaterials into medical devices as anti-infective coatings or surface modifiers. These modifications alter surface nanotopography and reduce microbial adhesion, ultimately preventing biofilm formation on commonly used biomedical implants [12,26,27].

Taken together, these developments highlight the practical potential of NP-based therapeutics as adaptable alternatives to conventional antibiotics. The present work focuses on their application against MDR pathogens and biofilm-associated infections, emphasizing the physicochemical advantages, versatility as nanodimensional drug carriers, and opportunities for functionalization and stimuli responsiveness. In addition, translational barriers and emerging strategies are discussed to prioritize approaches most likely to advance toward clinical implementation.

2. Nanoparticles for Antimicrobial Applications

2.1. Favorable Physicochemical and Biological Characteristics

Due to their nanoscale dimensions and unique physicochemical properties, NPs are increasingly applied across biological, pharmaceutical, and medical disciplines [1]. Their high surface area-to-volume ratio, tunable morphology, and surface reactivity collectively contribute to enhanced biological interactions, drug-carrying capacity, and therapeutic efficiency [15,19]. Surface engineering strategies, such as PEGylation, ligand conjugation, and charge modification, further enhance colloidal stability, biocompatibility, and cellular uptake, while enabling selective targeting, minimizing immune recognition, and promoting endocytosis or transcytosis mechanisms [19,20,28]. Functionalization with antimicrobial peptides, antibodies, or other targeting moieties can also increase NPs' pathogen specificity and reduce side effects [29-31]. Regarding antimicrobial resistance (AMR), many metallic and metal oxide NPs (e.g., silver, zinc oxide, copper oxide) exert direct bactericidal effects through oxidative stress induction, membrane disruption, and protein denaturation [18,32,33]. In contrast to conventional antibiotics, which act on specific metabolic or biosynthetic pathways and are prone to resistance, NPs exert multiple, simultaneous modes of action, reducing the probability of resistance emergence [29,30,33].

NPs also exhibit potent antibiofilm capabilities. Their small size and modifiable surfaces facilitate penetration into biofilm matrices, enabling EPS disruption and quorum sensing inhibition, leading to stronger effects on embedded bacteria [21,29,33]. This is particularly relevant for chronic and device-associated infections, where biofilm tolerance undermines conventional therapy [18].

Beyond plain NPs, bionano structured composites, such as hydrogels, polymeric coatings, wound dressings, and scaffolds, have demonstrated significant efficacy in preventing or treating localized infections [34,35]. These materials serve

as antimicrobial reservoirs while supporting wound healing and barrier functions. From a translational standpoint, the incorporation of NPs into environmental or surface-modifying applications has emerged as a critical strategy for infection prevention, particularly in nosocomial settings. NP-based coatings on high-touch surfaces (e.g., hospital doorknobs, bed rails, packaging) can inactivate pathogens upon contact and reduce nosocomial transmission [18,36,37].

2.2. Surface Functionalization of Nanoparticles

Surface functionalization is a pivotal strategy in NP engineering, enabling control over physicochemical behavior, biological compatibility, and targeted functionality. This process involves attaching various organic or inorganic moieties onto NPs' surface through non-covalent interactions (e.g., hydrogen bonding, electrostatic forces, van der Waals interactions) and covalent linkages (Fig. 1) [29,38]. The choice of functionalization strategy depends on the intended application, the stability requirements, and the molecular characteristics of both the NP core and the functionalizing agents [31].

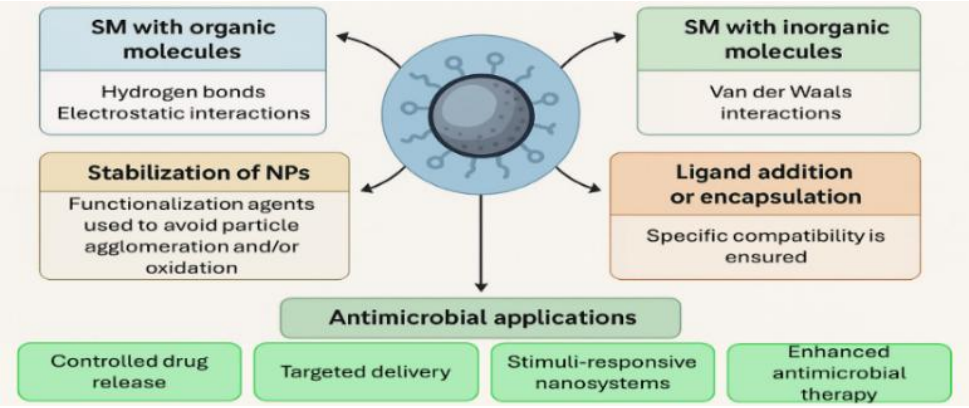

Fig. 1. Schematic overview of surface modification (SM) of nanoparticles.

Non-covalent functionalization offers simplicity and preserves biomolecule integrity, making it suitable for functions that require reversible or environmentally sensitive interactions. However, such systems are sensitive to environmental variables (e.g., pH, ionic strength, and temperature), limiting their stability and functionality [31,38]. Covalent approaches, by contrast, offer more durable linkages, commonly achieved via crosslinkers targeting carboxyl, amine, or thiol groups, facilitating stable conjugation of peptides, nucleic acids, or targeting ligands [29,31].

Functionalization serves several crucial roles in nanotherapeutic design, including stabilizing NPs against aggregation and oxidation, improving solubility and dispersion in biological fluids, enhancing the adsorption capacity of biomolecules, and directing the self-assembly of NPs into ordered structures or integration into composite materials [29,38]. A particularly promising surface engineering strategy is the development of stimuli-responsive nanosystems for

releasing therapeutic agents in response to specific internal (e.g., pH, redox potential, enzymatic activity) or external cues (magnetic fields, light, ultrasound, temperature) [24,25,39]. Such systems enable spatiotemporally controlled delivery, enhancing antimicrobial efficacy and minimizing systemic adverse reactions.

In antimicrobial therapy, active targeting appeared as a transformative approach, involving surface conjugation of targeting ligands that selectively recognize and bind to microbial markers such as cell wall polysaccharides, surface proteins, or lipid components overexpressed by pathogens [24,40-43]. Effective NP design requires optimization of ligand-receptor binding affinity, drug release kinetics, and conjugate stability [40]. Various biomolecules have been employed in active targeting strategies, including small molecules, peptides, monoclonal antibodies, nanobodies, aptamers, carbohydrates, and antimicrobial agents [44,45]. These targeting strategies enhance accumulation at the infection site, help circumvent off-target cytotoxicity, and reduce AMR selective pressure [45,46]. Several modification techniques, like encapsulation, ligand exchange, and the use of stabilizing agents, help tailor NPs' pharmacokinetics and biodistribution profiles [38]. These approaches are also influential in formulating hybrid systems (e.g., core-shell NPs, nanocomposites), which combine multiple functionalities in a single platform to enhance antimicrobial performance synergistically.

2.3. Inorganic Nanoparticles with Intrinsic Antimicrobial Activity

Inorganic NPs have attracted attention in biomedicine due to their dual role as nanobiocides (through innate antimicrobial activity) and as nanocarriers [22]. They offer cost-effectiveness, extended functional lifespan, thermal stability, and safety [47]. Among the most studied inorganic NPs are metal-based (Ag, Au, Cu), metal oxide-based (ZnO, TiO_2, MgO), and magnetic (Fe_3O_4) NPs [48,49]. Each type exhibits unique characteristics that define its antimicrobial action; however, efficacy is mainly attributed to the release of metal ions and the catalysis of reactive oxygen species (ROS). By damaging cellular membranes, proteins, and nucleic acids, NPs act against MDR pathogens and disrupt biofilm formation, making them up-and-coming alternatives to traditional antibiotics. However, prolonged or repeated exposure can induce bacterial resistance, necessitating the use of surface functionalization [23].

2.3.1. Silver NPs

AgNPs exhibit an extensive antimicrobial spectrum that spans Gram-positive and Gram-negative bacteria, demonstrating activity even against MDR pathogens [50]. Current evidence suggests that AgNPs induce cell membrane disruption, cytoplasmic leakage, and intracellular oxidative stress, with size, surface charge, and morphology playing crucial modulatory roles [51]. Smaller AgNPs, with larger surface-area-to-volume ratios, show enhanced antibacterial effects due to higher Ag^+ ion release and ROS production [52]. Polymeric coatings or capping

agents improve bioactivity and stability [53,54] but cytotoxicity towards mammalian cells remains a concern, necessitating careful dose optimization [55].

2.3.2. Gold NPs

AuNPs have tunable size, shape, and surface chemistry, allowing for tailored antimicrobial applications [56]. AuNPs interact electrostatically with teichoic acids in Gram-positive bacteria and lipopolysaccharides in Gram-negative bacteria, causing membrane disruption [57]. Their efficacy depends on strain, particle size, concentration, and surface functionalization [58]. Functionalization with biomolecules, proteins, or polymers enhances biocompatibility, bioavailability, target selectivity, and circulation half-life [59], though balancing antibacterial potency with toxicity is critical, especially at high doses [60,61].

2.3.3. Iron Oxide NPs

Iron oxide NPs (especially Fe_3O_4 and γ-Fe_2O_3) are valued for their magnetic properties, chemical stability, and low cytotoxicity, rendering them attractive for theranostic applications [38]. Their activity is driven by electrostatic adhesion to bacterial surfaces [62] and release of Fe^{2+}/Fe^{3+} ions, triggering Fenton-type ROS formation that damage DNA, lipids, and proteins [63,64]. They display broad-spectrum activity, with greater efficacy against Gram-negative species due to thinner cell walls and increased surface interaction [61].

2.3.4. Zinc Oxide NPs

ZnO NPs possess broad antimicrobial, antifungal, and antiviral activity, paired with biocompatibility and FDA "Generally Recognized As Safe" (GRAS) status [65,66]. Their nanoscale dimension augments the capacity to penetrate cellular membranes [67], while electrostatic interactions with microbial membranes result in membrane disruption, internalization, and release of Zn^{2+} ions, further interfering with metabolic pathways and generating ROS [68,69]. The acidic dissolution of ZnO NPs further enhances antimicrobial potency, yet controlling ion release and ROS generation is crucial to mitigate toxicity and enhance therapeutic windows [70].

2.3.5. Copper Oxide NPs

CuO NPs display significant antimicrobial, antifungal, and anti-biofilm activity, due to strong redox activity and structural affinity for microbial components [71], and ROS generation through Cu^{2+} ions release [72]. The high surface-area-to-volume ratio and crystalline structure of CuO NPs allow close membrane interaction, destabilizing bacterial cells and inhibiting essential processes. CuO NPs demonstrated activity against resistant pathogens and aquaculture bacteria, having potential for environmental and clinical contexts [61].

2.4. Nanoparticles as Carriers of Antimicrobial Agents

The clinical efficacy of antimicrobial agents is limited by low aqueous solubility, poor membrane permeability, and rapid elimination, with pharmacological outcomes hindered by suboptimal absorption, biodistribution,

metabolism, excretion, and therapeutic half-life [73]. In infectious diseases, these limitations translate into frequent or high-dose administrations, increased toxicity, resistance development, and patient non-compliance [74]. NPs overcome these barriers by encapsulating or adsorbing a variety of agents (e.g. hydrophilic and hydrophobic antibiotics, nucleic acids, proteins, and vaccine components) [18,75]. Their nanoscale size allows them to pass biological barriers, ensure intracellular delivery, and targeted drug release at the infection site [76].

2.4.1. Enhanced Drug Delivery and Antimicrobial Efficacy

NPs improve antimicrobial therapy through controlled and sustained drug release, biofilm penetration, and internalization into microbial cells—critical for persistent or chronic infections [21,75]. These nanoformulations are amenable to various administration routes, including oral, dermal, ocular, pulmonary, nasal, and intravaginal delivery, or they can be applied as coatings for biomedical devices and implants, modifying nanotopography and offering anti-infective abilities [12,26,27].

NP-based delivery vehicles operate via two main approaches: chemical and physical triggers for release. For instance, an example of chemical trigger-based drug release is when acidic environments associated with infection sites activate the liberation of encapsulated antibiotics from pH-sensitive nanocarriers. Other possibilities include internal physiological conditions like redox gradients or enzymatic activity that enable intracellular drug release via passive diffusion or endocytosis [41]. On the other hand, physically triggered release assumes the influence of external stimuli, such as magnetic fields, ultrasound, light, or thermal cues that modulate NP behavior, ensure spatiotemporal control, and improve targeting efficiency [16]. These smart nanocarriers (Fig. 2) are particularly useful in infection-targeted therapy, where inflammatory microenvironments and pathogen-specific markers can be exploited for responsive or triggered drug release, guaranteeing high local drug concentrations and minimal exposure for healthy tissues [46,77].

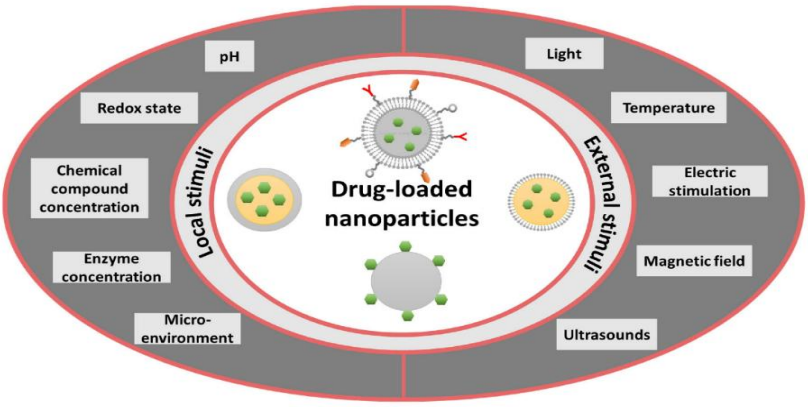

Fig. 2. Schematic overview of stimuli-responsive nanosystems. Reprinted from an open-access source [18].

2.4.2. Carrier Material Versatility

The versatility of NP carrier materials is pivotal in tailoring antimicrobial therapies to specific clinical needs. Recent advancements have introduced a diverse array of carrier materials, each offering unique advantages [18]. Among the broad class of nanoparticulate carriers, polymeric NPs have shown particular promise. These materials can function both as passive reservoirs and active antimicrobial agents owing to their surface charge, size, and degradation profiles. Importantly, polymer-based NPs can be engineered to exhibit pathogen-specific targeting, either passively through the enhanced permeability and retention (EPR) effect or actively via ligand-based targeting [44,77]. Biodegradable polymers like chitosan and poly(lactic-co-glycolic acid) (PLGA) have been extensively utilized, accounting for their favorable biocompatibility and controlled drug release capacity [18]. Moreover, the chemical tunability of polymers enables to develop nanocarriers for a wide spectrum of administration routes, including challenging options such as buccal, periodontal, and transdermal delivery, expanding the applicability of nanoantibiotics across medical and dental practice [77]. Lipid-based nanocarriers represent another interesting category of nanosystems for antimicrobial therapeutics delivery. Liposomes and solid lipid nanoparticles (SLNs) offer the advantage of encapsulating both hydrophilic and hydrophobic drugs. Their structural similarity to biological membranes facilitates cellular uptake, making them effective carriers for antimicrobial delivery [78]. Moreover, lipid-based nanosystems benefit from low clearances and the possibility of increasing therapeutics half-life in plasma [79], thus enhancing drug efficacy. A series of lipid-based nanovehicles have been reported to successfully deliver various antimicrobials, prolonging their blood circulation, improving bactericidal activity, and offering superior tolerability over free drugs [80,81].

Encouraging prospects also arise from a plethora of inorganic NPs. Besides the above-described metal and metal oxide-based nanomaterials recognized for their inherent antimicrobial properties, mesoporous silica nanoparticles (MSNs) have occupied a special place in recent research. The most representative advantage of MSNs is their high drug-loading capacity, which enables the delivery of sufficient drug amounts to effectively destroy target pathogens [82]. MSNs permit enhanced drug stability, with sustained and controlled drug release for ensuring long-term efficacy. MSN functionalization with polycationic dendrimers further enhances bacterial biofilm penetration [83]. In addition to the success of each category alone, hybrid nanocarriers draw increasing attention, leading to synergistic outcomes. Combining different materials can synergistically enhance nanocarriers' stability, drug-loading efficiency, and controlled release profiles. These hybrids can be tailored to respond to specific stimuli, allowing for targeted and controlled drug release at infection sites [18,78]. These carrier materials' continuous development

and optimization are essential for advancing NP-based antimicrobial therapies, offering customizable solutions to combat diverse and resistant infections.

2.4.3. Overcoming Resistance and Systemic Toxicity

Nanoencapsulation helps restore the efficacy of existing antimicrobials by protecting drugs from enzymatic degradation, bypassing efflux pumps, and enabling lower doses [84,85]. In addition, NPs can penetrate biofilms more effectively than free drugs through their small size and possible surface modifications, facilitating antibiotic delivery of antibiotics directly to the bacterial cells within the biofilm matrix [86,87]. Some nanocarriers act dually as drug vectors and antimicrobial agents ensuring synergistic antimicrobial therapy, and reducing the likelihood of developing resistance [86].

Functionalizing NP with ligands or antibodies allows for selective pathogens targeting, minimizing unwanted effects and lowering systemic toxicity. For example, magnetic NPs can be directed to infection sites using external magnetic fields, concentrating the therapeutic agent where needed [88]. Designing NPs that release their payload in response to specific stimuli ensures that the antimicrobial agent is released primarily at the infection site, reducing systemic exposure and associated toxicity [89]. By leveraging these strategies, NP -based drug delivery systems can enhance the efficacy of antimicrobial therapies, overcome resistance mechanisms, and minimize adverse effects, paving the way for more effective and safer treatments.

3. Current Challenges and Future Perspectives

Despite their promise inorganic NPs face some challenges that impede their widespread clinical and industrial translation. Comparing toxicity data across studies is difficult due to inconsistencies in NP characteristics, administration routes, dosing regimens, and frequency of exposure. Variability in NP purity, aggregation state, and biological matrices further complicate results extrapolation [90,91]. Physicochemical properties (i.e., particle size, geometry, surface area, charge, and hydrophobicity) critically influence their interaction with biological systems, with some formulations linked to impaired clearance, sustained inflammation, and fibrosis [61,90,91]. Thus, despite their versatile antimicrobial action, MDR efficacy, and easy functionalization, challenges remain regarding toxicity, resistance development, and standardization of inorganic NPs. Standardization of NP characterization and exposure protocols is therefore essential to safely translate inorganic nanomaterials into clinical use. Polymeric NPs, while offering high drug loading and biodegradability, may nonspecifically bind to negatively charged biological components such as non-target proteins or cell membranes, leading to cytotoxic effects and reducing transfection efficiency [41,77]. Similarly, polymeric micelles, which are valued for their modifiable architecture

and good tissue permeation, suffer from poor physical stability and the risk of premature cargo release under physiological conditions [92].

Lipid NPs, though exhibiting excellent biocompatibility and bioavailability, frequently display low drug encapsulation efficiency and are vulnerable to destabilization by environmental stimuli such as heat, radiation, pH fluctuations, or enzymatic degradation [16]. Exosomes, the most biologically derived nanocarriers, possess outstanding biocompatibility and immune evasion capabilities; still, their clinical translation is currently impeded by technical challenges related to isolation, scalability, and cargo stability [93,94]. For clarity, the advantages and disadvantages of each class of NPs have been visually represented in Fig. 3. Collectively, the existing limitations underscore the need for advanced engineering strategies (such as targeted surface functionalization and stimuli-responsive release systems) to optimize the therapeutic efficacy and biosafety of nanoparticle-based antimicrobial platforms.

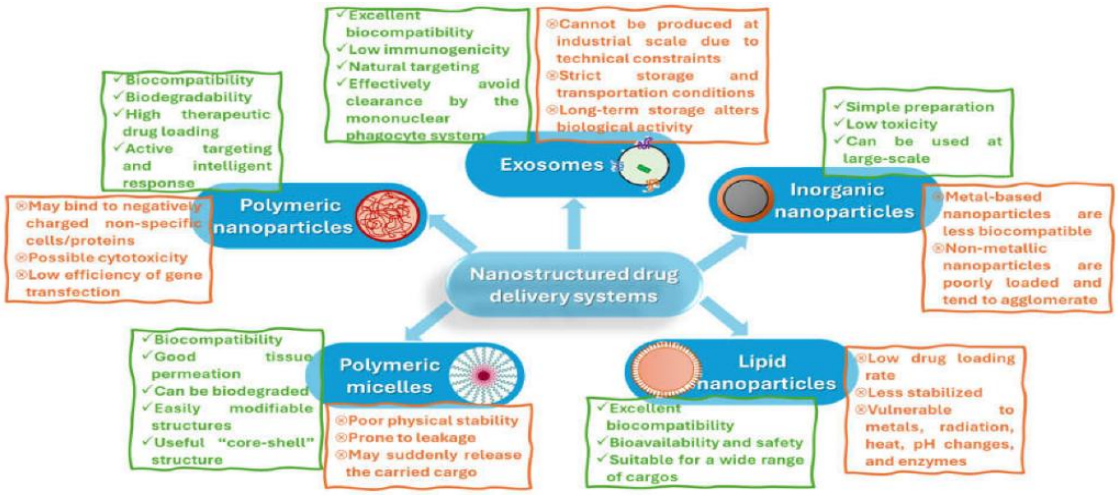

Fig. 3. Schematic overview of advantages and disadvantages of different nanostructured drug delivery systems. Reprinted from an open-access source [94].

Another important aspect of NP-based antimicrobial treatments is to ensure the preservation of commensal microbiota while targeting pathogens. The integration of narrow-spectrum nanoantibiotics or selective targeting ligands is essential for minimizing dysbiosis and supporting host health [95-97]. Hence, future strategies should focus on microbiome-conscious nanotherapeutics that differentiate between pathogenic and commensal bacteria to minimize dysbiosis and preserve host-microbe homeostasis.

A major priority moving forward is the development of new synthesis strategies that are safer and more sustainable than existing methods. Green synthesis routes—employing plant extracts, biopolymers, or microbial agents—have gained traction due to their environmental friendliness and the elimination of

hazardous byproducts [71,98,99]. These methods contribute to more biocompatible NPs that are suitable for long-term applications in humans and ecological systems.

Promising advances in antimicrobial nanomedicines have also been enabled through the continuous development of microfluidic synthesis platforms. Such emerging devices permit the precise, reproducible, and scalable fabrication of NPs. In contrast to conventional bulk methods, microfluidics enables fine-tuned control over NP size, shape, surface chemistry, and drug loading, which are all critical factors for ensuring consistent biological responses and minimizing batch-to-batch variability [100]. Furthermore, microfluidic systems offer continuous flow operation**,** reduced reagent consumption, and improved mixing efficiency**,** making them well-suited for green and high-throughput production of antimicrobial nanocarriers [101]. In addition, the recent progress of artificial intelligence and machine learning provides valuable tools for *in silico* prediction of nanomaterial–microbe interactions, optimization of nanocarrier composition, and high-throughput toxicity screening. These computational strategies may significantly reduce time and cost in preclinical development phases. Moreover, AI utilization can accelerate the design of tailored nanocarriers with reduced experimental burden, pointing toward the direction of precision and personalized medicine [102,103].

The ongoing emergence of AMR calls for multifunctional nanotechnological strategies. In this context, NPs act as carriers of antimicrobial agents and are increasingly integrated into broader therapeutic platforms, including antimicrobial photodynamic therapy (aPDT) [5,104,105]. However, the efficacy of aPDT varies based on microbial membrane composition. Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* show higher resistance attributed to the presence of lipopolysaccharide content on their outer membrane, often necessitating higher concentrations of photosensitizers than Gram-positive strains like *Staphylococcus aureus* and *Bacillus subtilis* [104,106]. For enhancing efficacy, scientists have recently proposed the utilization of photosensitizers conjugated with delivery vehicles based on inorganic NPs [107] or nanoscale covalent organic frameworks (NCOFs) [108], a strategy that does not seem to induce AMR. Looking ahead, NPs will play an integral role in the design of advanced, smart, and responsive biomedical devices. These include nanostructured coatings for implants and catheters [109,110], functional wound dressings with sustained antimicrobial activity [111,112], and antibacterial textiles for healthcare settings [72,113]. Additionally, inorganic nanoparticles hold promise in the development of next-generation disinfectants and active packaging systems for food preservation [114,115].

In conclusion, while the future of various NPs in antimicrobial applications is promising, systematic evaluation of long-term safety, resistance mitigation strategies, and regulatory harmonization is imperative. Integrating green synthesis,

stimuli-responsive designs, and material–microbe interaction insights will be central to advancing these nanomaterials toward clinical and environmental implementation.

4. Conclusions

NPs, through their tunable physicochemical and biological properties, are a promising platform for next-generation antimicrobial therapies. By enhancing drug bioavailability, target specificity, and therapeutic efficacy, they provide viable alternatives to conventional antibiotics in the fight against MDR pathogens. This work emphasizes their dual role as intrinsic antimicrobials and carriers of therapeutic agents, addressing critical barriers such as resistance and systemic toxicity. Moving forward, efforts should prioritize translational optimization, such as scalable synthesis, biosafety validation, and regulatory alignment to accelerate the clinical integration of nanoantibiotics into routine practice.

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