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NARRATIVE REVIEW

Antibiotic Resistance and Nanoparticles as Antimicrobial/Adjuvant Agents

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Abstract

Antibiotic resistance (AR) can affect human health through both therapeutic and preventative aspects. The therapeutic consequences are evident in treatment failures and complications, whereas the preventive implications are caused by restrictions on treatment options in immunosuppressive conditions. The effects of AR are severe and could potentially affect morbidity and mortality. AR results in prolonged infections and hinders the start of microbiologically effective treatment. Furthermore, due to the restricted options for treatment, individuals suffering from these diseases sometimes need the use of toxic drugs, endure prolonged hospital stays, or require surgical procedures. The overall impact of AR leads to increased morbidity and death rates, together with increased usage of resources and costs. Research has indicated that nanoparticles (NPs) possess properties such as charge, high surface area, and the capacity to transport substantial amounts of antibiotics or other substances. The specific size and shape make them optimal antibacterial agents. In addition to the essential antimicrobial properties of NPs, comprehensive studies indicate that their large surface area plays an important role in adhesion and rapid cell penetration. Nanomaterials exhibit enhanced interactions with bacteria and promote rapid killing, and NP-based treatments offer a highly promising solution to these problems. This review sheds light on the combined use of antibiotics with NPs, which can enhance inhibition and reduce the likelihood of resistance in microorganisms.

1. Introduction

Antimicrobial resistance (AMR) is the ability of microorganisms, such as bacteria, parasites, fungi, and viruses, to reproduce and grow despite the presence of drugs designed to kill them [1]. (AMR) has been identified by the World Health Organization (WHO) as one of the three greatest public health problems, and AMR infections have been considered the third-leading cause of mortality, following cardiovascular disorders [2]. The emergence of AMR was once considered a threat mainly affecting hospitals and healthcare facilities; however, over the past few years, resistant bacteria have proliferated in the community, resulting in a rise in both the populations at risk and the rate of resistant infections. (AMR) impacts almost every aspect of health, including human, animal, and environmental domains; hence, it implicates society as a whole [3].

Antimicrobial-resistant diseases were directly responsible for around 1.27 million deaths in 2019, while approximately 5 million deaths were subsequently associated with drug-resistant infections, as reported in an extensive study released in January 2022. By 2050, estimates suggest that this number will rise to 10 million annually, significantly surpassing the number of deaths attributed to cancer [4]. All microorganisms exhibit (AMR), a natural evolutionary phenomenon, by developing genetic alterations that enable them to withstand potentially lethal selection pressures. AMR is mostly acquired and transmitted through human-to-human interactions in various settings, including health care institutions and the community. Infections that result

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from antimicrobial-resistant organisms can be difficult to treat and significantly increase the risk of severe illnesses as well as death. Multiple types of antimicrobial drugs are available, including antibiotics, antifungals, antivirals, disinfectants, and food preservatives, which either inhibit microorganisms' growth and reproduction or eliminate them. Compared to other classes of antimicrobials, antibiotics are the most commonly used category and are specifically used to treat bacterial infections and antibiotic resistance (AR) [5].

2. Antibiotic Resistance Factors

The ability of organisms to survive when subjected to antibiotics that would typically kill them or disrupt their growth is referred to as AR [6]. The discovery of antibiotics and their subsequent introduction into clinical practice are regarded as one of the most significant turning points in the history of the healthcare industry. These drugs have prevented the deaths of millions of people from infections that would have been fatal in the past. Furthermore, they have made it possible to perform surgical procedures, organ transplants, care for premature newborns, and chemotherapy for cancer patients. Despite this, treating infections is becoming increasingly complicated due to the development of multidrug resistance (MDR) in the microorganisms that cause these diseases [7]. The improper use of antibiotics in clinical practice is a primary contributor to AR and is likely to threaten the significant advancements achieved by antibiotics in modern medicine, such as the prevention and treatment of life-threatening infections, cancer treatment, and developments in surgical approaches [8].

There are many factors, including human behavior, that can influence the emergence of antibiotic resistance (AR) (Figure 1); AR genes are found everywhere in natural ecosystems. Massive environmental reservoirs of antibiotic resistance (AR) genes have been generated by a wide variety of anthropogenic activities, including the use of antibiotics in agriculture and the presence of antibiotics in waste disposal facilities.[6] The use of antibiotics in the animal and food industries, the shortage of rapid detection procedures, and the presence of antibiotics in the environment are among the most important factors contributing to the development of AR [9].

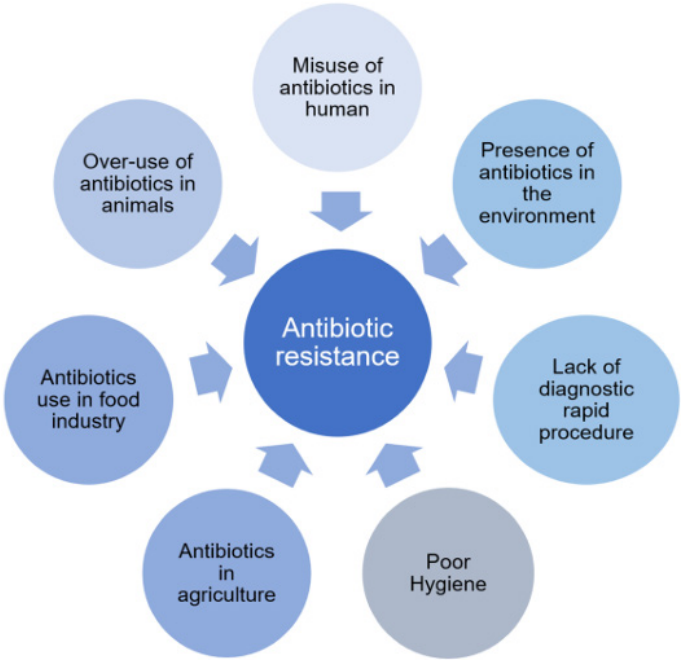

Figure (1): Factors of the development of AR.[8]

AR can affect human health through both therapeutic and preventive measures. The therapeutic consequences are evident in treatment failures and complications, whereas the preventive implications arise from restrictions on treatment options in immunosuppressive conditions, including invasive techniques such as inhalation or catheterization, sophisticated surgical procedures such as transplantation, and cancer treatment [10]. Clinically, when an antibiotic is introduced, all targeted pathogens remain susceptible; however, over time, bacteria gradually become resistant to it. From an evolutionary perspective, bacteria can either mutate their chromosomes to adapt to the effects of antibiotics or acquire foreign DNA that codes for resistance determinants through horizontal gene transfer (HGT). The hypothesis that the antibiotic-resistance gene or genes passed on to human pathogenic bacteria through HGT originate from ambient or commensal bacteria is strongly supported by data [11].

3. Types of AR

There are three major types of AR (Table 1):

1. Intrinsic resistance means that some bacteria could naturally resist certain types of antibiotics because they have specific genes in their DNA without needing to change or gain new ones. Intrinsic resistance means that if antibiotics are used to treat illnesses caused by certain bacteria, those bacteria will inevitably develop resistance to them. In terms of the mechanisms of drug. Intrinsic resistance involves both efflux pumps and decreased permeability. Additionally, it frequently impacts the multidrug efflux pumps [12].
2. Acquired resistance is the process by which bacteria that used to be vulnerable become resistant by getting a gene mutation or extra genetic material from other bacteria. HGT occurs primarily through three mechanisms: conjugation, transposition, and transformation. Plasmids obtained through conjugation often spread the acquired resistance, which can be either temporary or permanent [13].
3. The trait of adaptive resistance is reliant on changes in the environment and can be either interim or long-lasting, depending on its intensity and duration of selection pressure. Sub-inhibitory antibiotic doses, combined with environmental variables such as ion concentrations, pH, stress, growth factors, and nutrition, might affect bacterial growth (Figure 2) [14].

AR can develop in four main ways: transformation, transduction, conjugation, and mutation, and it can occur

Table (1): Taxonomy of Antibiotic Resistance Mechanisms.[17–19]

Resistance	Exemplar Pathogens	Molecular Basis	Clinical Implication
Intrinsic Resistance	*Pseudomonas aeruginosa* (β-lactams) *Mycobacterium tuberculosis* (macrolides) *Enterococcus faecalis* (cephalosporins)	Low outer membrane permeability, constitutive efflux pumps (MexAB-OprM), lack of drug target (no penicillin-binding proteins for specific antibiotics), enzymatic inactivation systems	Guides empirical therapy selection; certain antibiotic classes should never be used against specific organisms regardless of testing results
Acquired Resistance	*Staphylococcus aureus* (MRSA - mecA) *Klebsiella pneumoniae* (carbapenem-resistant - KPC, NDM-1) *Enterococcus* (VRE - vanA/vanB)	Plasmid-mediated β-lactamases (blaCTX-M, blaKPC, blaNDM), altered PBP2a preventing β-lactam binding, modified ribosomal targets (ermB for macrolides), aminoglycoside-modifying enzymes (AAC, ANT, APH)	Major driver of treatment failures; requires antimicrobial stewardship, infection control measures, and combination therapy strategies
Adaptive Resistance	*Pseudomonas aeruginosa* (biofilms, nutrient limitation) *Staphylococcus aureus* (small colony variants) *Mycobacterium tuberculosis* (persisters)	Stress response activation (stringent response, SOS response), reduced metabolic activity and growth rate, biofilm-associated gene expression, persister cell formation through toxin-antitoxin systems	Causes recurrent infections and treatment prolongation; not detected by standard susceptibility testing; requires extended antibiotic courses and biofilm-disrupting strategies

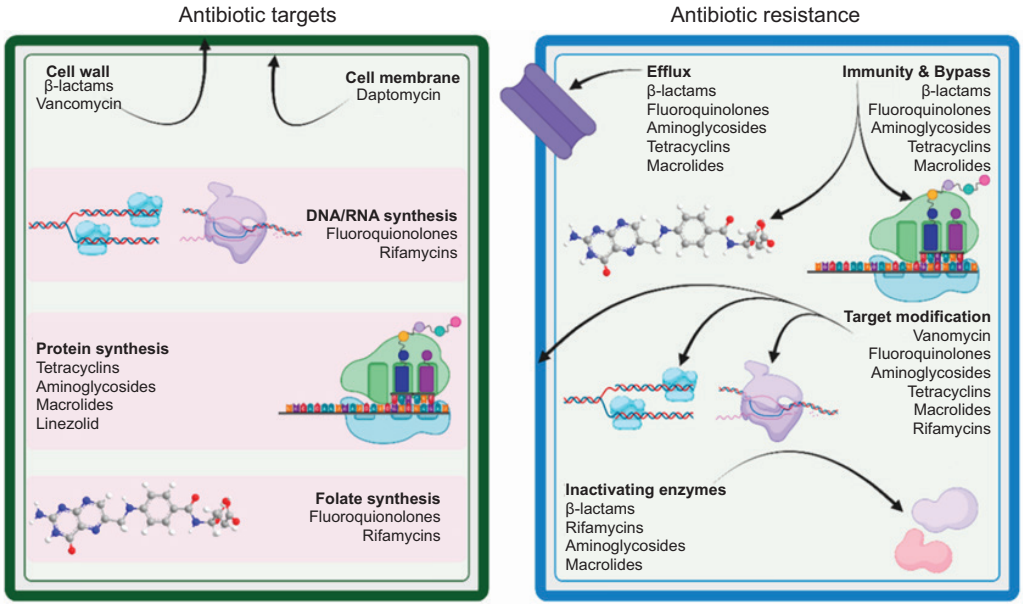

Figure (2): Targets of antibiotics and drug resistance mechanisms.[5]

through four different methods: blocking cell entry, pumping out the antibiotic, breaking down proteins, and changing the target [15]. Some methods may induce AR in one or two classes of antibiotics, while others produce MDR isolates, characterized by their resistance to three or more classes of antibiotics [9].

Mechanisms of (AR) have been known for a while, and genes associated with AR and resistance-encoding integrons have been identified in the gut microbiota of people who were not exposed to antibiotics and who appeared to be isolated from the modern world [6]. The Antibiotic-Resistant Gene Database already contains over 23,000 potential resistance genes across approximately 380 types, derived from accessible bacterial genome sequences [16].

4. Effects of Antibiotic Resistance

The effects of AR are severe and could affect morbidity and mortality (Figure 3) [6]. AR results in prolonged infections and hinders the start of microbiologically effective treatment. Furthermore, due to the restricted options for treatment, individuals suffering from these diseases sometimes need the use of toxic drugs, endure prolonged hospital stays, or require surgical procedures. The overall impact of AR leads to increased morbidity and death rates, together with increased usage of resources and costs [8].

The rate and frequency of bacterial infections resistant to antibiotics have reached alarming levels in the twenty-first century, posing an imminent danger to global public

health as a silent global epidemic, hence requiring urgent actions. The lack of new antibiotic discoveries and supplies to fight fatal infections caused by resistant microorganisms starkly contrasts with demand. Infections caused by antimicrobial-resistant organisms are not only challenging to treat but also significantly increase the risk of severe illness and mortality.[5] The infections remain among the main causes of fatality in the developing countries, along with the return of previously treated diseases due to AMR, which is also counted as a significant factor [8].

Infections are also a frequent consequence in cancer patients, who possess a threefold higher risk of falling victim to a deadly infection in comparison to non-cancer patients.[20] Infections are a primary or major contributor to the deaths of roughly Half of individuals with solid tumours or blood-related malignancies [21]. Although drug-resistant diseases are infrequently recorded as the definitive cause of death on death certificates [9]. A 2015 study revealed that 58 of 282 fatalities (23%) among cancer patients requiring critical care were associated with infections acquired in hospitals. A multidrug-resistant pathogen has been identified in 88% of the cases [22]. Moreover, multiple new studies confirm the connection between AR and complications in patients suffering from solid tumors and hematological malignancies [23]. Infection ranks as the second main cause of death among cancer patients. The decreased effectiveness of antibiotics caused by resistance from bacteria poses a threat to the continued effectiveness of cancer treatment. Infections are common in cancer patients, requiring the use of effective antibiotics for both prevention and treatment of bacterial infections. Antibiotic failure raises the risk of sepsis and death from sepsis in cancer patients.[9] The broad and prolonged prescription of broad-spectrum antibiotics to lower morbidity and death from infections in cancer patients likely promotes the development of resistance [24].

5. Factors of AR

Factors associated with antibiotic-resistant infections included comorbidities, prior antibiotic use, the presence of a urinary catheter, and a urinary tract infection source [25]. Moreover, cancer patients are susceptible to healthcare-associated infections, which represent a significant source of antibiotic-resistant organisms. Since the use of antibiotics or chemotherapy can lead to dysbiosis of the gut microbiota, which influences bacterial diversity [26].

The imbalance in gut microbiota may increase the risk of resistant bacteria, severe infections, post-transplant difficulties, and decreased efficacy in cancer patients having immunotherapy.[9] Additionally, most antibiotics administered in medical centers are broad-spectrum. These antibiotics usually show activity against several bacterial species rather than the specific pathogen targeted in a given patient situation [27]. As a result, both pathogenic and non-pathogenic commensal bacteria that comprise the typical microbiome develop AMR [28].

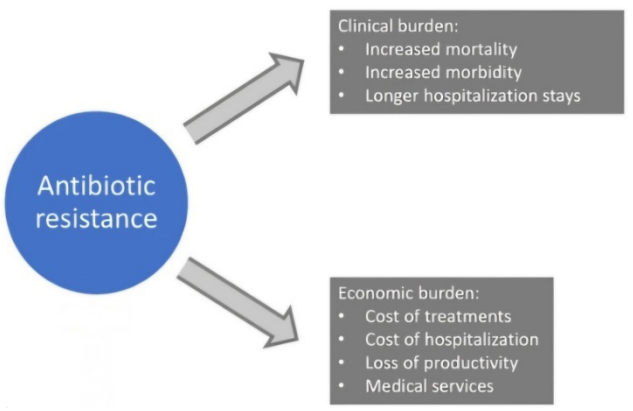

Figure (3): Clinical and economic impacts of AR.[8]

6. Nanotechnology

Nanotechnology focuses on the study of material properties at the nanoscale level. The Japanese scientist Norio Taniguchi coined the term "nanotechnology" in 1974 to describe the science of nano-sized particles. This science has established a platform for manipulating materials at the nanoscale, enabling the development of products with special qualities and multifunctionality. Nanomaterials already have numerous applications, including electronics, environmental science, energy harvesting, mechanical industries, bioremediation, and medicine. In medicine, they serve as potential tools for cancer treatment, delivering medicines, performing biomedical imaging, detecting pathogens, probing DNA, enabling tissue engineering, purifying biological molecules, and developing nanotherapeutics for bacterial infections [29].

Nanoparticles (NPs), usually defined as invisible small particles with diameters between 1 and 100 nanometers, possess significant importance in today's science. Nanoscale particles are atoms or molecular aggregates with a minimum of one dimension ranging from 1 to 100 nm, which may significantly modify their physicochemical properties in comparison to bulk materials. It can be composed of various bulk materials, and their behavior can be determined by both their chemical composition and particle size and morphology [30]. NPs can have many shapes, such as conical, spiral, flat, or hollow. They have unique physical characteristics that offer unusual mechanical strength, enhanced stability, and various other benefits [31]. NPs are receiving increased attention across multiple fields, including materials science, energy, health, and biotechnology [32]. NPs are also recognized for their optical, electrical, magnetic, and several other properties [33]. Optical properties are considered a unique trait of nanomaterials. These properties depend on the nanomaterials' tiny size, shape, and surface attributes, making them extremely useful in fields such as biomedicine, photoelectrochemistry, solar cell imaging, and optical detector design [34]. Research has indicated that NPs possess properties such as charge, high surface area, and the capacity to transport substantial amounts of antibiotics or other

substances [35]. The specific size and shape, make them optimal antibacterial agents. In addition to the essential antimicrobial properties of NPs, comprehensive studies indicate that their large surface area plays an important role in adhesion and rapid cell penetration [36].

Various structures of metal NPs have been identified, including rods, tubes, spheres, triangles, tetragons, pentagons, and hexagons. These structures are crucial for determining their interactions with microbial membranes or enzymes [37]. Furthermore, the high surface area versus volume ratio of these NPs makes them effective transport and antibacterial agents in various areas. Currently, there is a serious scientific investigation into NPs due to their possible uses in fields such as medical research, medicine delivery, wastewater treatment, optics, electronics, agriculture, and sensor support [38].

6.1. Types of nanoparticles

NPs are categorized into three types according to the source: engineered, natural, and incidental. The natural type of NPs has already existed since the dawn of the earth and continues to be present in nature (e.g., volcanic and lunar dust, mineral composites). The incidental type, also referred to as waste or human-made particles, is generated by human industrial processes such as welding emissions, coal burning, and diesel exhaust. The engineered type of NPs has attracted considerable attention for their beneficial effects on different industries, including consumer products, pharmaceuticals, transportation, energy, cosmetics, and agriculture. Engineered nanomaterials are categorized into four subtypes: carbon-based, metal-based, dendrimers, and composites [30].

1. Carbon-based nanomaterials: nanomaterials that contain carbon [39].
2. Inorganic-based nanomaterials: They include metals and metal oxide nanomaterials such as Ag, Au, Cu, and Zn.
3. Organic-based nanomaterials: These primarily consist of organic materials like dendrimers, liposomes, micelles, and polymer NPs.
4. Composite-based nanomaterials: multiphase nanomaterials that have one phase in the form of a nanoscale dimension, along with other bulk materials [40].

The inorganic material category is further divided into materials that are metal-based and materials that are metal oxide-based. Metal-based NPs are made from metals like gold, copper, selenium, and silver and are used in areas such as improving radiotherapy, transferring genes, and thermal ablation. Metal oxide-based materials are, as indicated by their names, produced through the process by which a metallic material oxidizes when oxygen is present. Silicon dioxide is one of the primary examples of the single metal oxide category, along with zinc oxide, titanium dioxide, and magnesium oxide. Fields like healthcare, agriculture, electronics, information technology, energy, and environmental preservation utilize these materials due to their unique characteristics [41]. The dimensions and morphology of oxide particles can be altered by adjusting parameters such as pH, ionic strength, and various temperatures [42].

6.2. Antimicrobial NPs

The main reason for the failure of antimicrobial drugs, along with their limitations, is due to the AMR shown by bacteria. Additionally, antimicrobials often have poor water solubility, low oral bioavailability, instability, inaccurate targeting of the infection, and high toxicity; they can be challenging for patients to adhere to because frequent use is required. So, researchers are now focusing on developing new antimicrobial agents to overcome the shortcomings of traditional medications [43]. For the last thirty years, no new medication has been introduced for commercial use. Therefore, there has been a search for different approaches to combat pathogens [38]. The use of nanotechnology in the management of infectious diseases stems from its unique properties, which make it highly reactive [29]. The NPs created from various metal oxides showed toxicity towards bacterial cells by easily penetrating the cell wall, accelerating the generation of ROS, or degrading the enzymes within the bacterial cell wall, which results in cell death [32]. Furthermore, metals and metal salts that form NPs display toxicity to microorganisms at minimal concentrations, effectively eliminating them by attaching to and deactivating intracellular proteins (Table 2) [44].

NPs with antimicrobial properties operate through a range of microbiological mechanisms that enable them to combat bacterial pathogens and overcome AR patterns. One of the most prominent of these mechanisms is the production of reactive oxygen species (ROS). Silver nanoparticles (AgNPs) induce oxidative stress by increasing intracellular accumulation of free radicals, including superoxide, hydroxyl radicals, and hydrogen peroxide. A direct correlation has been found between elevated ROS levels and increased antibacterial activity against Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa [45]. Membrane disruption also contributes to bacterial cell killing. Electrostatic interactions neutralize the negative charge of the cell membrane by the positively charged NPs, increasing its permeability and causing leakage of cellular components. Studies have shown that amine-functionalized silver NPs, approximately 5 nm in size, exhibit high charge- and size-dependent efficacy in targeting cell walls and disrupting membrane integrity [46]. The release of metal ions represents an additional mechanism, known as the "Trojan horse" mechanism, in which NPs release active ions (such as Ag^{+}) into the cellular environment, disrupting protein and DNA synthesis while maintaining a long-lasting antimicrobial effect [47]. NPs also play an effective role in inhibiting biofilm formation by penetrating the extracellular polymeric matrix and disrupting cell-cell communication pathways (Quorum sensing). This gives them an advantage over conventional antimicrobials in dismantling the complex structure of biofilms and eliminating the bacterial cells within them [48]. Finally, studies have shown that synergism between NPs and antibiotics is a promising strategy, as combining AgNPs with antibiotics reduced the

Table (2): Nanoparticle classes, antimicrobial mechanisms, and target pathogens

NP class	Primary mechanisms	Target pathogens	Evidence tier	Key references
Silver (Ag)	• ROS generation (O_2, OH, H_2O_2) • Ag^+ ion release • Membrane disruption • DNA/protein damage • Efflux pump inhibition	*E. coli*, *S. aureus* (including MRSA), *P. aeruginosa*, *K. pneumoniae*, *Salmonella* spp., *C. albicans*	High (extensive in vitro/in vivo)	45,46,49
Gold (Au)	• Membrane depolarization • ATP synthase disruption • ROS generation (moderate) • Electrostatic membrane interaction • Antibiotic delivery vehicle	*E. coli*, *B. subtilis*, multi-drug resistant uropathogens, MRSA (when functionalized)	Moderate-High (requires surface functionalization)	51–53
Copper Oxide (CuO)	• Cu^{2+} ion release (Fenton-like) • Strong ROS generation • Membrane lipid peroxidation • Protein carbonylation • DNA strand breaks	*E. coli*, *S. aureus*, *P. aeruginosa*, *B. subtilis*, *Salmonella* spp.	High (potent broad-spectrum)	54
Zinc Oxide (ZnO)	• Zn^{2+} ion release • Photocatalytic ROS generation • Membrane disruption • Internalization and intracellular damage • Efflux modulation	*E. coli*, *S. aureus*, *P. aeruginosa*, *L. monocytogenes*, *Streptococcus* spp.	High (photo-enhanced activity)	55,56
Magnesium Oxide (MgO)	• Surface hydroxylation → ROS • Alkaline stress (pH increase) • Membrane disruption • Mg^{2+} ion release (minimal toxicity) • Enhanced by Zn-doping	*E. coli*, *S. aureus*, *Bacillus* spp., *Xanthomonas oryzae*, MDR strains	Moderate (biocompatible, less cytotoxic)	56,57
Polymeric (Chitosan, PLGA)	• Polycationic membrane disruption • Outer membrane disassembly • Efflux pump modulation • Controlled antibiotic release • Mucosal adhesion enhancement	*E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, biofilm-associated infections	High (excellent drug carriers)	58,59
Liposomal	• Membrane fusion delivery • Targeted drug accumulation • Efflux pump bypass • Sustained release • Reduced systemic toxicity	*Mycobacterium* spp., *P. aeruginosa* (CF infections), *Acinetobacter* spp., intracellular pathogens	High (clinically approved formulations)	60,61

minimum inhibitory concentration (MIC) by up to 32-fold against multiresistant bacteria from the ESKAPE group. This effect is attributed to a complementary action: the NPs weaken the bacteria's defense barriers, while the antibiotics target their internal biological processes [49].

Nanomaterials show enhanced interactions with bacteria and promote quick killing, and NP-based treatment offers a highly promising solution to these problems (Figure 4). Hence, the combined use of antibiotics with NPs can improve inhibition effectiveness and reduce the likelihood of resistance among organisms [50]. Nanomaterials also displayed excellent solubility, stability, and biocompatibility when used with targeting agents; they can be adjusted to specific pH levels, light, and heat conditions. Nanomaterials have efficacy against a wide spectrum of microorganisms [29].

These nanomaterials, particularly NPs, offer a wide range of antibacterial activity toward Gram-negative and Gram-positive bacteria, viruses, fungi, bacteriophages, and algae. Two primary methods for using NPs as antimicrobial agents include:

1. Directly fighting antimicrobial drug resistance.
2. Act as carriers for the delivery of traditional antimicrobials.

Research has demonstrated that NPs can infiltrate microbial cells by causing damage to their membranes, initiate internal antimicrobial actions such as the production of reactive oxygen species (ROS), modify DNA/RNA and proteins, deactivate enzymes, enhance the removal of substances by boosting efflux pumps, reduce cell permeability, release metal ions, and prevent biofilm formation. Factors such as chemistry, particle size and morphology, surface-to-volume ratio, and zeta potential influence the antibacterial action of NPs [43].

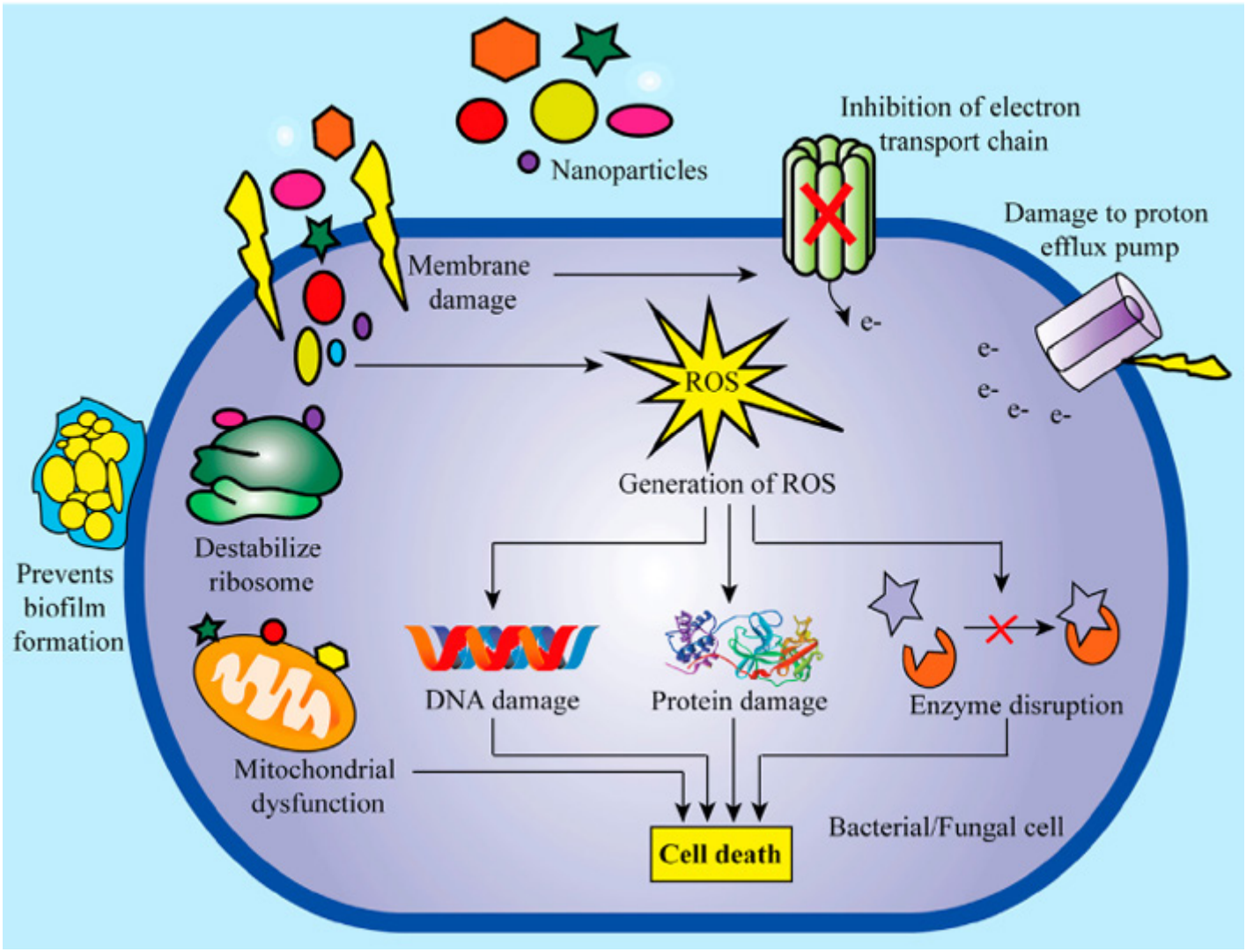

Figure (4): Antimicrobial mechanisms of various nanoparticles.[38]

7. Conclusion

AR affects human health in both preventive and therapeutic ways, leading to problems and treatment failures. Long-term infections may develop, making therapy less effective and necessitating harsher medications, extended hospital stays, or surgery. A possible remedy for AR is provided by NPs because of their charge, large surface area, and capacity to carry antibiotics. Antibiotics and NPs together can increase the efficiency of inhibition and decrease microbial resistance, which may lower rates of morbidity and death.

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Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

Contributor Role	Degree of Contribution		
	Lead	Equal	Supporting
Conceptualization	AHK	HAO	
Data curation	AHK		
Formal analysis	AHK	HAO	
Funding acquisition	AHK		
Investigation	AHK	HAO	
Methodology	AHK	HAO	
Project administration	HAO		
Resources	AHK		
Software	AHK		
Supervision	HAO		
Validation	HAO		
Visualization	HAO		
Writing-original draft	AHK		
Writing-review & editing	AHK	HAO	

Ethical Approval

The study was approved by the relevant ethics committee. Informed consent was obtained from all participants.

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