

Innovative Approaches to Combating Antibiotic Resistance: The Role of Metal Oxide Nanoparticles

Gülen Melike DEMİRBOLAT*, Müjde ERYILMAZ***, Bindia JUNEJO***

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Antibiyotik Direnciyle Mücadelede Yenilikçi Yaklaşımlar: Metal Oksit Nanopartiküllerinin Rolü

SUMMARY

Antibiotic resistance is an increasing global health problem that requires innovative strategies beyond traditional antibiotic therapies. The rise of multidrug-resistant bacteria has made many standard antibiotics ineffective, underscoring the need for alternative antimicrobial agents. With their unique physicochemical properties, nanoparticles (NPs) have attracted significant attention in the pharmaceutical sector. Among these, metal oxide nanoparticles (MONPs) have gained substantial attention due to their unique physicochemical properties, broad-spectrum antimicrobial activity, biocompatibility, and ability to target multidrug-resistant pathogens. This review explores the potential of MONPs as innovative alternatives to combat antibiotic-resistant bacteria. These NPs exert antimicrobial effects through multiple mechanisms, including the formation of reactive oxygen species, disruption of bacterial membranes, and inhibition of essential enzymes, ultimately leading to bacterial cell death. In addition to their direct bactericidal effects, MONPs exhibit significant potential in biofilm penetration and inhibition, a crucial feature since biofilms significantly contribute to bacterial resistance. Furthermore, MONPs demonstrate synergistic interactions with conventional antibiotics, potentially reducing the required dosage and associated side effects of these drugs. Despite their therapeutic potential, the use of MONPs is limited due to concerns about toxicity to human cells and environmental impact. This review provides a comprehensive analysis of MONPs as alternative antimicrobial agents, detailing their mechanisms of action, applications in combating antibiotic resistance, and recent advances in nanoparticle design to improve safety profiles. By highlighting the opportunities and challenges of MONPs, this review seeks to contribute to developing more effective therapies against antibiotic-resistant infections and insights into their future clinical applications.

Keywords: Antimicrobial agents, antibiotic resistance, biofilm inhibition, metal oxide nanoparticles, nanotechnology.

ÖZ

Antibiyotik direnci, geleneksel antibiyotik tedavilerinin ötesinde yenilikçi stratejiler gerektiren, giderek önem kazanan küresel bir sağlık sorunudur. Çoklu ilaç direnci gelişen bakterilerin artışı, birçok standart antibiyotiğin etkisiz hale gelmesine yol açmış ve alternatif antimikrobiyal ajanlara olan ihtiyacı daha da ön plana çıkarmıştır. Nanopartiküller (NP'ler), fizikokimyasal özellikleri nedeniyle farmasötik alanda oldukça dikkat çekmektedir. Bu nanopartiküller arasında metal oksit nanopartiküller (MONP'ler), benzersiz fizikokimyasal özellikleri, geniş spektrumlu antimikrobiyal aktiviteleri, biyouyumlulukları ve çoklu ilaç direnci gösteren patojenleri hedef alma yetenekleri sayesinde büyük ilgi uyandırmaktadır. Bu derleme, antibiyotik dirençli bakterilerle mücadelede yenilikçi alternatif yaklaşım olarak MONP'lerin potansiyelini incelemektedir. Bu nanopartiküller; reaktif oksijen türlerinin (ROS) oluşumu, bakteriyel membranların bozulması ve temel enzimlerin inhibisyonu gibi çoklu mekanizmalar yoluyla antimikrobiyal etki gösterir. Doğrudan bakterisidal etkilerinin yanı sıra MONP'ler, biyofilmlere penetrasyon ve biyofilm oluşumunun inhibisyonunda da önemli potansiyele sahiptir. Ayrıca MONP'ler, konvansiyonel antibiyotiklerle sinerjik etki göstererek gerekli antibiyotik dozunun ve buna bağlı yan etkilerin azaltılmasına katkı sağlayabilir. İnsan hücreleri üzerinde toksisite ve olumsuz çevresel etki, terapötik potansiyellerine rağmen MONP'lerin kullanımını sınırlamaktadır. Bu derleme, MONP'lerin antimikrobiyal ajanlar olarak alternatif rolüne kapsamlı bir bakış sunmakta; etki mekanizmalarını, antibiyotik direnciyle mücadeledeki uygulamalarını ve güvenlik profillerini iyileştirmeye yönelik nanopartikül tasarımındaki son gelişmeleri ele almaktadır. MONP'lerin sunduğu olumlu yönlerin yanında karşılaşılan zorlukları da vurgulayarak, antibiyotik dirençli bakterilerin neden olduğu enfeksiyonlara yönelik daha etkili tedavilerin geliştirilmesine katkıda bulunmayı ve gelecekteki klinik uygulamalar için rehber olmayı amaçlamaktadır.

Anahtar Kelimeler: Antimikrobiyal ajanlar, antibiyotik direnci, biyofilm inhibisyonu, metal oksit nanopartiküller, nanoteknoloji.

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* ORCID: 0000-0001-5621-5818, Department of Pharmaceutical Technology, Faculty of Pharmacy, Acibadem Mehmet Ali Aydınlar University, Istanbul, Türkiye

** ORCID: 0000-0003-3760-1996, Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Acibadem Mehmet Ali Aydınlar University, Istanbul, Türkiye

*** ORCID: 0000-0002-9997-6913, Food Quality & Safety Research Institute, PARC-Southern Zone Agricultural Research Centre, Karachi 75270, Pakistan

INTRODUCTION

Antimicrobials, including antibiotics, antivirals, antifungals, and antiparasitics, play a fundamental role in preventing and treating infections in humans, animals, and plants. Among these, antibiotics specifically target bacterial infections and have been crucial in managing bacterial diseases. However, the overuse and misuse of antibiotics across various sectors have led to one of the most pressing global health challenges: antibiotic resistance. This escalating crisis has resulted in increased morbidity and mortality rates, rising healthcare costs, and significant strain on healthcare systems worldwide. The World Health Organization (WHO) has recognized antibiotic resistance as a top global priority due to its potential to disrupt healthcare systems, compromise surgical procedures, and reduce the effectiveness of critical therapies for life-threatening diseases such as tuberculosis and pneumonia (GBD 2021 Antimicrobial Resistance Collaborators, 2024; Ventola, 2015; WHO, 2014).

According to the Review on Antimicrobial Resistance (AMR), the rising prevalence of drug-resistant infections poses a significant global health and economic threat (GBD 2021 Antimicrobial Resistance Collaborators, 2024). It is estimated that, if left unaddressed, AMR could result in 10 million deaths annually by 2050, surpassing the mortality rates of diseases such as cancer. This staggering projection underscores the urgent need for coordinated global action to mitigate the spread of resistance, develop new antibiotics, and implement effective strategies to preserve the efficacy of existing treatments (O'Neill, 2016). Given that the COVID-19 pandemic has caused approximately 7.1 million deaths globally, the projection of 10 million deaths annually from AMR by 2050 highlights the critical urgency of addressing this escalating threat (WHO, 2025a). Inappropriate use of antibiotics is an additional clinical challenge, and antibiotic resistance is one of the new global health concerns. The prediction that AMR could lead to 10 million deaths

annually by 2050 was made before the onset of the globally devastating COVID-19 pandemic. Before the pandemic, considerable progress had been made in reducing deaths from resistant infections through robust prevention measures, as reported by the Centers for Disease Control and Prevention (CDC). However, COVID-19 significantly hindered efforts to combat AMR. Healthcare systems were overwhelmed during the pandemic, leading to a surge in antibiotic use, often inappropriately for suspected bacterial infections in COVID-19 patients, even though most cases are viral. This unregulated antibiotic use weakened antibiotic stewardship programs, particularly for patients presenting with COVID-19-like symptoms. The unprecedented patient volumes in hospitals, especially critically ill individuals requiring prolonged ventilator support, further strained infection control practices. These challenges collectively led to a rise in healthcare-associated resistant infections, exacerbating the already critical issue of AMR. The CDC reported substantial increases in infections caused by healthcare-associated pathogens, including carbapenem-resistant *Acinetobacter*, extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, vancomycin-resistant Enterococcus (VRE), and drug-resistant *Candida*. Resistant hospital-onset infections and associated deaths both increased at least 15% during the pandemic's first year. Furthermore, reduced access to healthcare services delayed AMR testing and data reporting, weakening surveillance systems (CDC, 2022).

According to the 2025 WHO Global Antibiotic Resistance Surveillance Report, approximately 17% of laboratory-confirmed bacterial infections worldwide are caused by antibiotic-resistant pathogens, with the highest resistance rates observed in South-East Asia and Eastern Mediterranean regions. Alarming, carbapenem resistance in *Acinetobacter* spp. has reached 54.3%, and fluoroquinolone resistance in *Neisseria gonorrhoeae* exceeds 75%, highlighting the urgent need for novel antimicrobial strategies like nanotechnology-based therapeutics (WHO, 2025b).

To address the growing challenge of AMR, the WHO has established a Global Action Plan with five strategic objectives: (i) improving awareness and understanding of AMR through effective communication, education, and training; (ii) strengthening the knowledge and evidence base through surveillance and research; (iii) reducing the incidence of infection through effective sanitation, hygiene, and infection prevention measures; (iv) optimizing the use of an-

timicrobial medicines in human and animal health; and (v) promoting sustainable investments in new medicines, diagnostic tools, vaccines, and other interventions (Figure 1.). These objectives provide a comprehensive strategy for combating AMR. A 'One Health' approach, which integrates human and veterinary medicine, agriculture, and environmental management, is essential for implementing this plan effectively (WHO, 2022).

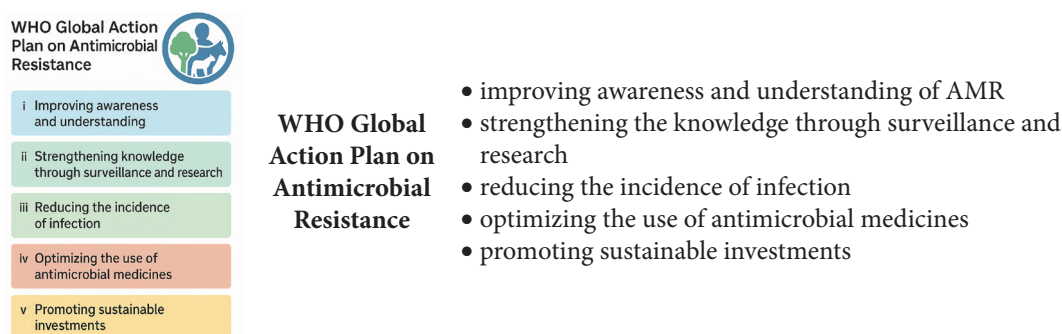


Figure 1. Strategic objectives of the WHO Global Action Plan on Antimicrobial Resistance

As bacterial pathogens continue to evolve, the effectiveness of conventional antibiotics diminishes, underscoring the urgent need for innovative antimicrobial strategies. In recent years, advancements in nanotechnology have provided promising alternative solutions to address the limitations of existing antibiotics. Nanoparticles (NPs), ranging in size from 1 to 100 nanometers, have emerged as versatile tools due to their unique physicochemical properties (Ozdal & Gurkok, 2022). Due to their innate antibacterial properties, metal oxide nanoparticles (MONPs) have been thoroughly investigated as possible remedies for multidrug-resistant (MDR) bacteria. They are considered among the most promising and reliable alternatives to current antibiotics (Monika et al., 2025). Among these, MONPs have emerged as potent alternatives, offering promising solutions to the challenges posed by antibiotic-resistant bacteria. Characterized by a high surface area-to-volume ratio, enhanced reactivity, and stability, MONPs also offer the potential for targeted drug delivery. These properties position MONPs as effective agents against antibiotic-resistant bacterial strains. Research has demonstrated that

MONPs such as zinc oxide (ZnO), titanium dioxide (TiO₂), silver oxide (Ag₂O), copper oxide (CuO), magnesium oxide (MgO), iron oxide (Fe₃O₄), cerium oxide (CeO₂), and aluminum oxide (Al₂O₃) exhibit broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria. They exert antimicrobial effects through multiple mechanisms, including the induction of oxidative stress, disruption of bacterial cell membranes, and inhibition of key microbial enzymes, making them highly effective against drug-resistant pathogens. Beyond their direct bactericidal effects, MONPs can penetrate and disrupt biofilms, which are protective bacterial communities that are notoriously difficult to eliminate in clinical settings (Flieger et al., 2024; Franco et al., 2022; Gautam et al., 2024; Gudkov et al., 2022a; Hancharova et al., 2024; Jiang et al., 2024; Nazem et al., 2024; Shandhiya et al., 2024; Zheng et al., 2024). MONPs provide less harmful, broad-spectrum, green alternatives to antibiotics. Although they may find use in biomedicine and agriculture, their resistance mechanisms, like genetic mutation and oxidative stress adaptation, are comparable to those of traditional antibiotics (Ngoepe

et al., 2025). Biofilms not only significantly contribute to the progression of diseases but also pose a formidable challenge to treatment efficacy. They create a highly protective environment that shields bacteria from major external stressors, including the host's immune response and antibiotics, thus limiting the effectiveness of available treatments (Aboelenin et al., 2024). By disrupting biofilms, MONPs enhance the efficacy of existing antibiotics and facilitate bacterial eradication. Additionally, MONPs have exhibited synergistic effects when combined with conventional antibiotics, enabling the use of lower antibiotic doses. This synergy not only reduces the risk of adverse side effects but also minimizes the likelihood of further resistance development. However, challenges such as cytotoxicity to human cells and potential environmental concerns remain barriers to their widespread clinical adoption. Addressing these concerns through biocompatibility optimization and controlled synthesis methods will be critical for the safe and effective implementation of MONPs (Franco et al., 2022; Gautam et al., 2024; Hancharova et al., 2024; Jiang et al., 2024; Nazem et al., 2024; Shandhiya et al., 2024). In summary, ad-

vancements in nanotechnology have positioned MONPs as a versatile and promising solution to antibiotic resistance. This review provides a comprehensive analysis of MONPs as alternative antimicrobial agents, focusing on their mechanisms of action, applications in combating antibiotic resistance, and recent advancements in nanoparticle design to enhance safety profiles. By addressing both the opportunities and challenges of MONPs, this review aims to contribute to the development of more effective therapies for antibiotic-resistant infections and offer insights into their future clinical applications.

MECHANISMS OF ANTIBIOTIC RESISTANCE

Antibiotic resistance arises from various mechanisms that bacteria employ to evade the action of antimicrobial agents, thereby threatening the effectiveness of current treatment strategies. These resistance mechanisms can be broadly categorized into five main types: (i) reduced permeability, (ii) efflux pump activity, (iii) enzymatic inactivation, (iv) target modification, and (v) target bypass (Mohanty et al., 2021) (Figure 2.).

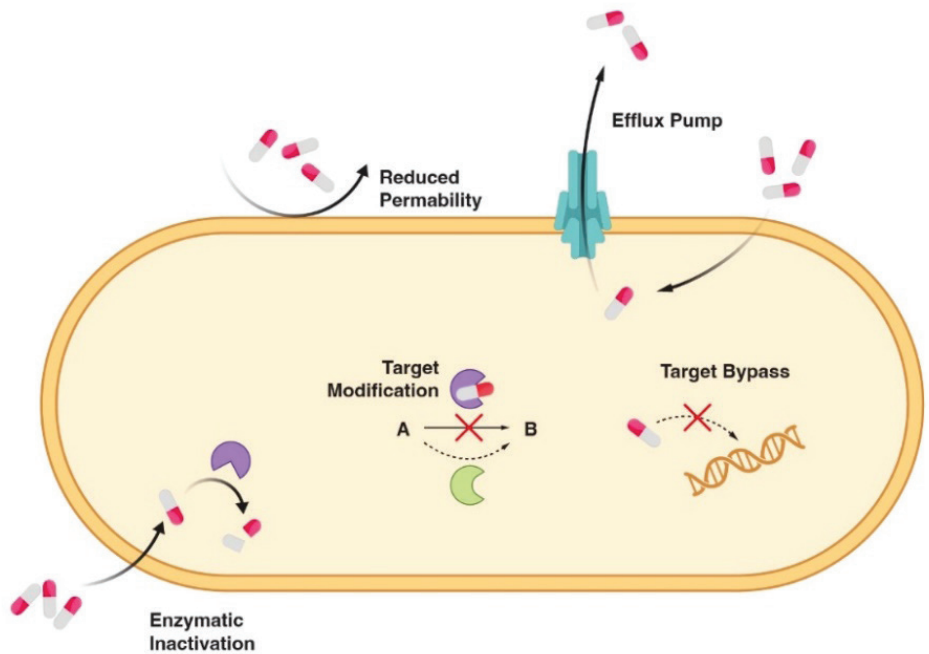


Figure 2. Mechanisms of antibiotic resistance

Bacteria can diminish the intracellular concentration of antibiotics by altering their membrane permeability. For example, mutations in porin proteins, such as the loss of OprD in *Pseudomonas aeruginosa*, restrict the entry of carbapenems, preventing the antibiotic from reaching its target site and rendering it ineffective (Hancock, 1998; Nikaido, 2003). ESBLs and carbapenemases are particularly concerning due to their broad activity against multiple drug classes (Singh & Kim, 2025). Efflux pumps are another critical mechanism contributing to antibiotic resistance. These protein complexes actively expel antibiotics from bacterial cells, reducing intracellular drug concentrations and thereby decreasing antibiotic efficacy. Efflux pumps are often encoded by genes located on mobile genetic elements, allowing bacteria to resist multiple antibiotic classes. For example, the overexpression of efflux pumps is a major resistance mechanism in multidrug-resistant pathogens such as *Acinetobacter baumannii* and *Klebsiella pneumoniae* (Li et al., 2015; Poole, 2005). One of the most common resistance mechanisms is the enzymatic degradation of antibiotics. Bacteria produce enzymes, such as β -lactamases, that hydrolyze the β -lactam ring of antibiotics, thereby inactivating their antimicrobial properties. Examples include ESBLs and carbapenemases, such as KPC, VIM, and NDM, which are highly prevalent in *Enterobacteriaceae* (Bush & Jacoby, 2010; Pitout & Laupland, 2008). Bacteria can also develop resistance by modifying antibiotic binding sites, thereby reducing the drug's ability to interact with its target. For example, alterations in penicillin-binding proteins (PBPs) confer resistance to β -lactam antibiotics, while mutations in DNA gyrase or topoisomerase IV contribute to fluoroquinolone resistance (Fisher et al., 2005; Hooper, 2000). Another significant resistance mechanism involves the bypassing of metabolic pathways targeted by antibiotics. For example, resistance to sulfonamides is achieved by acquiring plasmid-mediated genes that encode alternative dihydropteroate synthase enzymes, enabling the synthesis of folate via an alternate route (Sköld, 2000). These re-

sistance mechanisms often act synergistically, making infections caused by resistant pathogens increasingly challenging to treat. Furthermore, horizontal gene transfer through plasmids, transposons, and integrons facilitates the rapid dissemination of resistance genes, exacerbating the global antimicrobial resistance crisis (Martínez et al., 2007; Partridge et al., 2009). The rapid evolution of these resistance strategies underscores the urgent need for innovative solutions. MONPs, with their unique multi-target mechanisms such as oxidative stress induction, cell membrane disruption, and enzyme inhibition, represent a promising approach to overcoming bacterial resistance. By targeting critical resistance mechanisms, including efflux pump activity and enzymatic degradation, MONPs enhance the efficacy of conventional antibiotics. This dual capability positions MONPs as a critical tool in the global fight against antibiotic resistance (Altun et al., 2021; Hancharova et al., 2024; Jiang et al., 2024; Medic et al., 2024).

NANOPARTICLES AS INNOVATIVE ANTI-BACTERIAL AGENTS

NPs have emerged as innovative agents in combating bacterial infections due to their nanoscale size and unique physicochemical properties. Their high surface area-to-volume ratio, adjustable surface chemistry, and multifunctional capabilities equip them to address the complex mechanisms underlying antibiotic resistance. These characteristics make NPs highly effective in antimicrobial applications (Khorsandi et al., 2021; Rai et al., 2016). The antibacterial efficacy of NPs is primarily influenced by their synthesis conditions, including the type of reducing agent, temperature, concentration, and solvent, all of which play a key role in determining their biological properties (Horikoshi & Serpone, 2013; Qing et al., 2018). Additionally, physicochemical factors such as chemical composition, shape, size, and size distribution significantly affect their activity against bacterial pathogens (Shobha et al., 2014). Moreover, external environmental factors, including temperature, pH

levels, metal ion concentration, cell age, and reaction time, also contribute to their antimicrobial properties (Jaworski et al., 2018).

NPs exert their antimicrobial effects through multifaceted mechanisms, including membrane disruption, oxidative stress induction, and enzyme inhibition, making them effective against a broad spectrum of bacterial pathogens, including multidrug-resistant strains (Pelgrift & Friedman, 2013). Among various types of NPs, noble metal NPs, including silver (Ag), gold (Au), zinc (Zn), selenium (Se), and platinum (Pt), have demonstrated significant potential in biomedical applications, particularly in diagnosing and treating severe conditions such as cancer, HIV, tuberculosis, and Parkinson's disease. For instance, silver nanoparticles (AgNPs) are particularly notable for their antimicrobial properties, gold nanoparticles (AuNPs) serve as efficient drug delivery carriers, and platinum nanoparticles (PtNPs) are increasingly utilized in bone allografts and dentistry. These unique properties make NPs effective tools for addressing persistent challenges posed by multidrug-resistant (MDR) pathogens by enhancing drug absorption, enabling targeted delivery, and minimizing side effects. Moreover, NPs can act synergistically with antibiotics by targeting multiple bacterial components, including cell membranes, enzymes, and biofilms, thereby enhancing antibiotic efficacy. Organic NPs, owing to their biodegradability and biocompatibility, offer safer alternatives for therapeutic applications (Khorsandi et al., 2021; Rai et al., 2016). In recent years, green synthesis methods utilizing biological sources and waste materials have gained attention for producing

biocompatible and environmentally friendly NPs. For instance, green-synthesized AgNPs not only exhibit antibacterial activity but also show antifungal, antiviral, and anticancer properties, making them valuable in wound healing, pollutant degradation, and targeted drug delivery systems (Majeed et al., 2023; Sharma et al., 2022). In practical applications, studies have demonstrated the strong antibacterial efficacy of AgNPs integrated into natural fibers. For example, cotton fibers coated with AgNPs have been shown to achieve antimicrobial rates exceeding 99% with minimal Ag content (3 mg/g), highlighting the potential for precise nanoparticle integration and controlled dosing (Xu et al., 2017). These advancements position NPs as versatile and innovative agents in the global fight against antibiotic resistance, bridging the gap between traditional therapies and emerging antimicrobial challenges.

METAL OXIDE NANOPARTICLES: A STRATEGIC APPROACH TO COMBAT ANTIBACTERIAL RESISTANCE

MONPs have emerged as promising antimicrobial agents due to their nanoscale size, high surface-to-volume ratio, and unique physicochemical properties. These features enable MONPs to penetrate bacterial cell walls and biofilms, enhancing their bactericidal activity (Raghunath & Perumal, 2017). Several studies have reported the antibacterial activity of different MONPs against both Gram-positive and Gram-negative bacteria. Reported MIC values and inhibition zone diameters vary depending on the nanoparticle type and the bacterial species tested (Table 1.).

Table 1. Antibacterial activity of metal oxide nanoparticles (MONPs) against Gram-positive and Gram-negative bacteria

MONPs	Bacteria	MIC (mg/mL) / Inhibition zone (mm)	Reference
ZnO NPs	<i>Staphylococcus aureus</i>	3.9 mg/mL	Alekish et al., 2018
	<i>Escherichia coli</i>	31.25 mg/mL	
	<i>S. aureus</i>	5 mg/mL	
	<i>Staphylococcus epidermidis</i>	0.63 mg/mL	Junejo et al., 2023
	<i>Enterococcus faecalis</i>	10 mg/mL	
	<i>B. subtilis</i>	5 mg/mL	
	<i>E. coli</i>	5 mg/mL	
	<i>Klebsiella pneumoniae</i>	5 mg/mL	
	<i>S. aureus</i>	20 mm	Abo-Shama et al., 2020
	<i>E. coli</i>	26 mm	
	<i>Salmonella spp.</i>	15 mm	
TiO ₂ NPs	<i>S. aureus</i>	0.02 mg/mL	Thakur et al., 2019
	<i>E. coli</i>	0.01 mg/mL	
	<i>K. pneumoniae</i>	0.02 mg/mL	
Ag ₂ O NPs	<i>S. aureus</i>	0.05 mg/mL	Khatun et al., 2015
	<i>E. coli</i>	0.05 mg/mL	
	<i>S. aureus</i>	0.25 mg/mL	Yousef et al., 2025
	<i>E. coli</i>	0.25 mg/mL	
	<i>Salmonella typhimurium</i>	0.03 mg/mL	
	<i>Pseudomonas aeruginosa</i>	0.13 mg/mL	
MgO NPs	<i>S. aureus</i>	6.3 mm	Fatiqin et al., 2021
	<i>E. coli</i>	6 mm	
Fe ₃ O ₄ NPs	<i>S. aureus</i>	5 mg/mL	Flieger et al., 2024
	<i>S. epidermidis</i>	5 mg/mL	
	<i>Micrococcus luteus</i>	2.5 mg/mL	
	<i>Bacillus cereus</i>	5 mg/mL	
	<i>E. faecalis</i>	5 mg/mL	
	<i>S. typhimurium</i>	5 mg/mL	
	<i>E. coli</i>	5 mg/mL	
	<i>K. pneumoniae</i>	5 mg/mL	
CeO ₂ NPs	<i>P. aeruginosa</i>	0.0125 mg/mL	Zamani et al., 2021
Al ₂ O ₃ NPs	<i>S. aureus</i>	0.01 mg/mL	Hassan et al., 2024
	<i>E. coli</i>	0.01 mg/mL	
Co ₃ O ₄ NPs	<i>S. aureus</i>	5 mg/mL	Junejo et al., 2023
	<i>E. faecalis</i>	1.25 mg/mL	
	<i>B. subtilis</i>	5 mg/mL	
NiO NPs	<i>S. epidermidis</i>	10 mg/mL	Junejo et al., 2023
	<i>E. faecalis</i>	10 mg/mL	
	<i>B. subtilis</i>	5 mg/mL	
CuO NPs	<i>S. aureus</i>	5 mg/mL	Junejo et al., 2023
	<i>S. epidermidis</i>	1.25 mg/mL	
	<i>E. faecalis</i>	1.25 mg/mL	
	<i>B. subtilis</i>	2.5 mg/mL	
	<i>E. coli</i>	2.5 mg/mL	
	<i>K. pneumoniae</i>	2.5 mg/mL	

The antimicrobial efficacy of MONPs is attributed to several key mechanisms, including the generation of reactive oxygen species (ROS), membrane disruption, and the release of metal ions, all of which contribute to bacterial cell death. The ROS generated by MONPs induces oxidative stress in bacterial cells, damaging vital cellular components such as proteins, lipids, and DNA. This oxidative damage compromises the integrity of the bacterial cell membrane, leading to increased permeability and eventual cell lysis. Another important mechanism is the release of ROS, which can disrupt essential bacterial processes such as enzyme function and nutrient transport. Additionally, MONPs effectively disrupt bacterial biofilms, which are often resistant to conventional antibiotics. Bio-

films protect bacteria by forming a thick extracellular matrix that blocks the penetration of antimicrobial agents. However, the small size and high surface reactivity of MONPs allow them to penetrate biofilms, disrupting the matrix and eliminating embedded bacteria. MONPs, including ZnO, TiO₂, Ag₂O, CuO, MgO, Fe₃O₄, CeO₂, and Al₂O₃, have demonstrated broad-spectrum antimicrobial efficacy against planktonic bacteria and biofilm-associated infections, making them invaluable tools in combating multi-drug-resistant pathogens (Flieger et al., 2024; Franco et al., 2022; Gautam et al., 2024; Gudkov et al., 2022a; Hancharova et al., 2024; Jiang et al., 2024; Nazem et al., 2024; Shandhiya et al., 2024; Zheng et al., 2024) (Figure 3.).

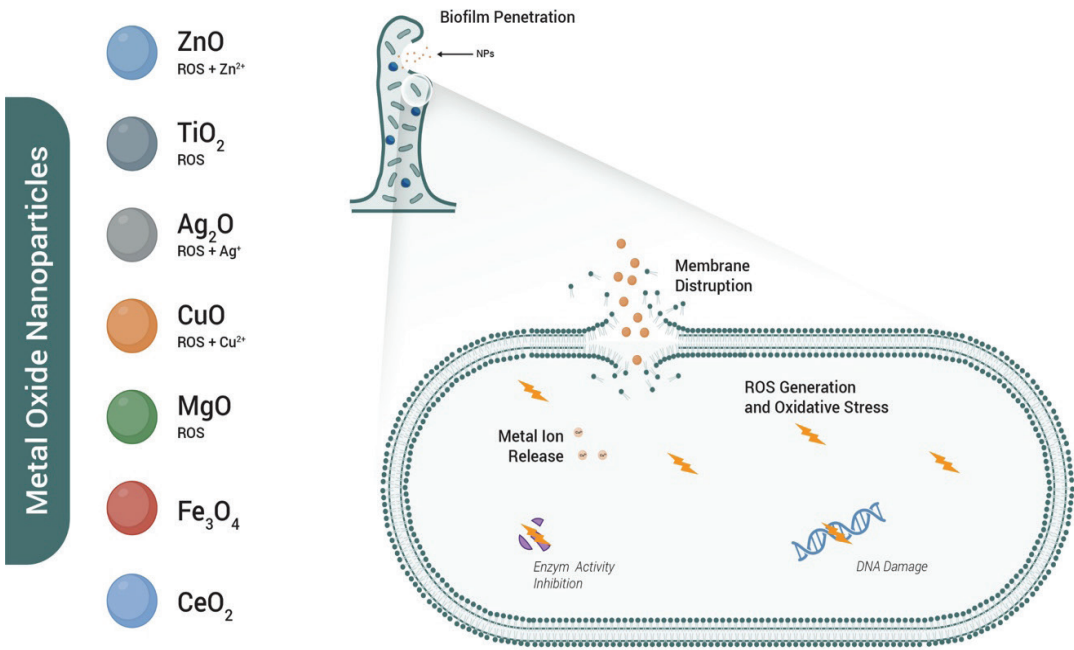


Figure 3. Mechanisms of metal oxide nanoparticles

Each type of MONP exhibits unique antimicrobial mechanisms. ZnO NPs are among the most extensively studied due to their strong antibacterial properties, which arise from ROS generation and zinc ion (Zn²⁺) release (Asif et al., 2024; Raghupathi et al., 2011). ZnO NPs release zinc ions (Zn²⁺), which disrupt bacterial metabolism by interfering with enzyme function and

nutrient transport pathways (Caron et al., 2024). ZnO NPs also exhibit significant biofilm inhibition properties, preventing the development of persistent bacterial colonies that are resistant to conventional antibiotics (Elzahaby et al., 2023).

Junejo et al. (2023) reported that Co₃O₄, CuO, NiO, and ZnO NPs possess antibacterial activity

against both Gram-positive and Gram-negative test bacteria. Among all tested MONPs, the best MIC value was observed with ZnO NPs against *Staphylococcus epidermidis* ATCC 12228. The biofilm inhibition percentages of NiO, CuO, Co_3O_4 , and ZnO NPs were reported as 88.5%, 85.95%, 80.35%, and 83.99%, respectively. These results highlight the multifunctional nature of MONPs in combating both planktonic and biofilm-associated bacterial populations, supporting their potential as alternative strategies against antibiotic-resistant microorganisms.

TiO₂ NPs leverage their photocatalytic properties to generate ROS under ultraviolet (UV) or visible light, leading to bacterial membrane disruption and intracellular damage. This light-induced antimicrobial activity makes TiO₂ NPs particularly useful in environmental disinfection and medical device coatings (Haque et al., 2024). Recent studies have shown that TiO₂ NPs are effective against biofilm-forming pathogens like *Staphylococcus aureus* and *P. aeruginosa*, reducing biofilm biomass and bacterial adhesion (Wasa et al., 2021). Ag₂O NPs have garnered significant attention for their potent antimicrobial and antibiofilm properties. Studies have demonstrated that Ag₂O NPs exhibit broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, including multidrug-resistant strains. Their mechanisms of action involve the generation of ROS and the release of silver ions, which disrupt bacterial cell walls, interfere with intracellular functions, and ultimately lead to cell death (Gudkov et al., 2022b; Mohanaparameswari et al., 2024). Additionally, Ag₂O NPs have been shown to inhibit biofilm formation by preventing bacterial adhesion and disrupting established biofilms, making them promising candidates for combating persistent infections associated with biofilm-producing pathogens (Elyamny et al., 2021).

Similarly, CuO NPs effectively inhibit bacterial growth and biofilm formation, particularly in multidrug-resistant pathogens such as methicillin-resistant *S. aureus* (MRSA), *Escherichia coli*, *K. pneumoniae*,

and *P. aeruginosa*, and *Acinetobacter* spp. The antibacterial mechanism of CuO NPs is primarily attributed to the generation of ROS and the release of Cu²⁺ ions, which disrupt bacterial membranes, proteins, and DNA, ultimately leading to cell death. Moreover, CuO NPs have been shown to significantly reduce biofilm biomass and bacterial adhesion in a concentration-dependent manner, making them effective against persistent infections associated with biofilm-producing pathogens. These findings underscore the potential of CuO NPs as a versatile and promising alternative to combat antimicrobial resistance and biofilm-associated infections (Khairy et al., 2024; Mengesha et al., 2024).

MgO NPs are increasingly recognized for their exceptional antimicrobial properties and broad biomedical applications. Due to their high surface area, biocompatibility, and reactive nature, MgO NPs are effective against a wide range of pathogens, including antibiotic-resistant bacteria. Their antimicrobial mechanisms include the generation of ROS, disruption of bacterial cell membranes, and release of magnesium ions, all of which interfere with bacterial survival and biofilm formation. These properties make MgO NPs promising candidates for combating persistent infections caused by biofilm-forming bacteria such as *S. aureus* and *P. aeruginosa*. Furthermore, the low toxicity and FDA-recognized safety of MgO contribute to its applicability in biomedical fields, including wound healing, tissue engineering, and drug delivery systems. By targeting bacterial resistance mechanisms and biofilms, MgO NPs offer a novel and sustainable solution to address the global challenge of antimicrobial resistance (Anić et al., 2018; FDA 2021; Gatou et al., 2024).

Fe₃O₄ NPs are emerging as promising antibacterial agents due to their biocompatibility, magnetic properties, and multiple mechanisms of antimicrobial activity. The antibacterial effects of Fe₃O₄ NPs are primarily attributed to their ability to generate ROS via Fenton or Fenton-like reactions. ROS, such as

hydroxyl radicals and superoxide anions, cause oxidative stress, leading to damage of bacterial DNA, proteins, and lipids, ultimately resulting in bacterial cell death. Additionally, Fe_3O_4 NPs adhere to bacterial cell walls and membranes through electrostatic and van der Waals interactions, leading to membrane disruption and leakage of cellular content. Fe_3O_4 NPs are particularly effective against both planktonic bacteria and biofilm-forming pathogens, which are notoriously difficult to treat with conventional antibiotics. Their ability to disrupt biofilms and enhance bacterial membrane permeability makes them viable candidates for combating multidrug-resistant (MDR) bacteria. Surface modifications, such as coating with polymers like chitosan or doping with foreign metals (e.g., Ag or Au), further enhance their antibacterial efficacy while improving biocompatibility and stability. For example, chitosan-coated Fe_3O_4 NPs have demonstrated significantly enhanced antimicrobial effects due to increased bacterial membrane interactions. Moreover, external magnetic fields can amplify their antibacterial performance by facilitating targeted delivery and localized hyperthermia effects, providing an innovative approach to treat persistent infections (Javanbakht et al., 2016; Zhang & Miao, 2024).

CeO_2 NPs have gained significant attention as promising antimicrobial agents due to their unique physicochemical properties and multifaceted mechanisms of action. The antibacterial activity of CeO_2 NPs is primarily linked to their ability to generate ROS, such as hydroxyl radicals ($\bullet\text{OH}$) and superoxide anions (O^{2-}), which cause oxidative stress in bacterial cells. This oxidative stress damages essential biomolecules like proteins, lipids, and DNA, leading to bacterial cell death. A distinctive property of CeO_2 NPs is their dynamic $\text{Ce}^{3+}/\text{Ce}^{4+}$ redox cycling and oxygen vacancy formation, which enhances their catalytic activity. These properties allow CeO_2 NPs to mimic natural enzymes like superoxide dismutase (SOD) and catalase, further amplifying their antimicrobial effect. Additionally, CeO_2 NPs can physically interact with bacterial membranes, disrupt biofilms, and inhibit

nutrient transport, contributing to their broad-spectrum antibacterial efficacy. Studies have also highlighted their photocatalytic properties, where visible or ultraviolet light activates CeO_2 NPs, generating additional ROS and enhancing their bactericidal activity. This feature makes CeO_2 NPs particularly effective against both planktonic and biofilm-associated bacterial pathogens. Given their low cost, biocompatibility, and high stability, CeO_2 NPs offer a sustainable alternative to conventional antibiotics and hold immense potential for addressing antimicrobial resistance (Sarif et al., 2022; Zheng et al., 2024).

Al_2O_3 NPs are gaining significant attention as antimicrobial agents due to their unique physicochemical properties, such as high mechanical strength, chemical stability, and large surface-to-volume ratios. Although Al_2O_3 NPs are traditionally considered inert and less reactive compared to other metal oxides like ZnO , TiO_2 , and CuO , recent studies have demonstrated their antibacterial and biofilm-inhibiting potential, particularly at high concentrations. The primary mechanisms of antibacterial action include electrostatic interactions between the positively charged Al_2O_3 NPs and the negatively charged bacterial cell walls, leading to membrane damage and disruption of bacterial integrity. Additionally, Al_2O_3 NPs generate ROS, which cause oxidative stress, lipid peroxidation, and DNA damage, ultimately resulting in bacterial cell death. Al_2O_3 NPs have demonstrated a bacteriostatic effect against Gram-positive and Gram-negative bacteria, including multi-drug-resistant strains like *S. aureus* and *P. aeruginosa* (Gudkov et al., 2022a; Hassan et al., 2024). The morphology and size of Al_2O_3 NPs are critical factors influencing their antibacterial efficacy; smaller and rod-like particles exhibit enhanced activity due to their increased reactivity and interaction with bacterial surfaces. Moreover, surface modifications, such as functionalization with polymers like chitosan, have been shown to enhance the antibacterial efficiency of Al_2O_3 NPs by facilitating better adherence to bacterial surfaces and controlled release properties. These composite materials exhibit improved bacteri-

cidal effects, particularly when targeting biofilm-associated infections. While their antibacterial effects are promising, further studies are needed to address toxicity concerns, optimize their synthesis, and explore their potential in clinical applications (Hassan et al., 2024). The synthesis and formulation of MONPs can be tailored to optimize their antimicrobial efficacy by manipulating factors such as particle size, shape, and surface chemistry. Recent studies have demonstrated that combining MONPs with antibiotics can enhance antibacterial efficacy, even against multidrug-resistant strains. These findings suggest that the synergistic use of MONPs and antibiotics holds promise for developing more effective treatments against resistant bacterial infections (Abo-Shama et al., 2020).

NANOPARTICLE DEPICTION AND SPECIFICITY TOWARDS ANTIBIOTIC RESISTANCE: RECENT ADVANCES

A fundamental classification of nanoparticle synthesis covers top-down and bottom-up approaches, and they both have their specific pros and cons. After the production, nanoparticle characterization is another key step to ensure that they can reach the target of a specific application. Characterization tests are usually performed using various methods, such as dynamic light scattering (DLS), UV-Vis spectroscopy, Fourier transform infrared spectroscopy (FT-IR), scanning electron microscope (SEM), transmission electron microscope (TEM), X-ray diffraction (XRD), etc. Thus, the particle size and distribution, zeta potential, optical properties, the chemical bonds on the surface of the nanoparticle, shape, and crystal structure can be enlightened (Erdoğan et al., 2019; Joshi et al., 2023; Negrescu et al., 2022; Ogbezode et al., 2023). Here, we focused on the relationship between the nanoparticle design and antimicrobial efficacy.

MONPs have garnered significant attention in the pharmaceutical industry due to their high stability, simple preparation methods, and tunable properties, including size, shape, and porosity. Due to their nanoscale size, MONPs can interact more effectively

with cellular structures than their bulk counterparts, enhancing their penetration into bacterial cells and biofilms (Negrescu et al., 2022).

Particle size plays a pivotal role in determining the extent of antimicrobial efficacy, with smaller particles exhibiting enhanced effectiveness (Erdoğan et al., 2025). It was reported that while ZnO MONPs with 2 μm – 12 nm of particle size showed antimicrobial properties, smaller ZnO NPs with 12 nm showed enhanced biocidal activity compared to larger ZnO NPs (2 μm). The increased bacterial growth inhibition could be achieved with smaller ZnO NP. Similarly, ultrafine TiO_2 (~20 nm) particles had longer clearance times and greater translocation to interstitial sites and regional lymph nodes than fine TiO_2 (~200 nm). This phenomenon is possibly a result of the greater surface area of MONPs. The large surface area increased the production of ROS and resulted in bacterial cell damage. MgO NPs also showed size-dependent bactericidal degree. Smaller MgO NPs (30–50 nm) showed larger inhibition zones for both Gram-positive and Gram-negative bacteria. On the other hand, MgO NPs with 70-130 nm expressed antimicrobial effects on only Gram-negative bacteria (Curwin & Bertke, 2011; Gold et al., 2018). The nanoscale size of these particles also allows for better penetration through biofilms, a common defense mechanism in many pathogenic bacteria. The nano-formulations' small size, large surface area, and highly reactive nature allow them to penetrate biological barriers such as biofilm and have a high selectivity for bacterial cells (Abdellatif et al., 2021; Sharma et al., 2019; Ramasamy & Lee, 2016). The increased surface area of MONPs makes it easier to load medications, while the MONPs' sizes are tiny enough to penetrate biofilms and microbial cell walls. Additionally, they are quickly excreted through the kidney and have extended plasma half-lives (Lee et al., 2019).

Another important factor in the design of MONPs is related to their surface charge, which is characterized by their zeta potential. MONPs can possess pos-

itive, negative, or neutral charges depending on the ionic charges or functional groups of the substances if the coating or surface modification is on the table. MONPs with the strongest positive charge demonstrate the most effective antibacterial properties, followed by those with neutral and then negative charges (Tamilselvi et al., 2024). Arakha et al. (2015) compared the Fe_3O_4 NPs with negative charged (n-IONP) and chitosan-coated Fe_3O_4 NPs with positive charged (p-IONP). It was indicated that n-IONP showed insignificant antimicrobial activity against *Bacillus subtilis* and *E. coli*, while p-IONP caused a significant antimicrobial effect by stimulating the ROS production. Although MONPs exhibit broad-spectrum antimicrobial activity by affecting both Gram-positive and Gram-negative bacteria, the surface charge of MONPs might be a significant parameter for the level of efficacy. El-Sadda et al. (2023) compared the catechol-based polyurethane foam polymer (PCPU) with lower negative charge and catechol-modified polyurethane foam with ZnO NPs (PCPU/ZnO) with higher negative charge. PCPU/ZnO showed a higher antibacterial effect against Gram-negative *E. coli* than PCPU, while PCPU had a higher antibacterial effect against Gram-positive *B. cereus*. Since bacterial cell walls have a negative charge due to the presence of acidic compounds such as peptidoglycan, Gram-positive bacteria with high peptidoglycan content (ie, with high negative charges) exert a greater repulsion toward PCPU/ZnO NPs, which may cause a lower antibacterial activity. On the other side, the antibacterial effect of PCPU/ZnO NPs was higher against *E. coli* due to lower repulsion forces. The surface of MONPs can be modified with charged groups in order to increase their antibacterial potential, but also to improve their biocompatibility. Rajiv et al. (2024) investigated MgO NPs functionalized with chitosan, an organic biopolymer, to further enhance the biocompatibility and therapeutic potential of MgO. Because chitosan has cationic properties, ie, positively charged, it interacts with the negatively charged cell wall of bacteria, causing the disruption of its integrity. MgO NPs

coated with chitosan boosted their antibacterial effect against both Gram-positive (*S. aureus*, *S. pneumonia*) and Gram-negative bacteria (*K. pneumonia*, *E. coli*).

Their surface can be easily tailored; in addition to enhancing biocompatibility, it is possible to selectively design MONPs for bacterial cells by functionalizing their surface with various ligands. Thus, the therapeutic agents carried by MONPs are delivered directly to the site of infection so that the treatment becomes more efficient in the ideal dosage range while the likelihood of drug degradation, potential side effects, and off-target effects reduces (Abd El-Aziz et al., 2022; Liu et al., 2019; Wang et al., 2020; Wasef et al., 2021). The antibacterial activity of MONPs can be impacted by the surface characteristics of NPs, which can change how the MONP interacts with the bacterial cell. Depending on the modifier's properties, different surface modifications can change the antibacterial impact. Additionally, the modifier is linked to the toxicity mechanism. The surface of ZnO NPs was modified with (3-glycidyloxypropyl) trimethoxysilane (GPTMS) so that the aqueous stability of ZnO NPs was promoted and the dispersion in water could be obtained. Moreover, the effect of surface modification on antimicrobial activity was evaluated (Lallo da Silva et al., 2019). Although the use of GPTMS led to an increase of the MIC against *S. aureus* and *E. coli*, there were no cytotoxic signals on the HaCat cell line at the maximum concentrations tested. Thus, the developed ZnO NP were not toxic to the human cell, but to the bacterium. Moreover, the toxicity was reported as selective for prokaryotes because the antimicrobial activity found in yeast was low. Additionally, their potential for targeted drug delivery systems opens new avenues for personalized medicine. However, addressing toxicity, regulatory hurdles, and environmental considerations remains crucial. Nanotechnology has established itself as a dynamic and interdisciplinary branch of research in recent years (Mohanpuria et al., 2008; Wang et al., 2021).

To another approach, the conjugation of other antimicrobials with MONPs makes bacteria more sensitive, thus it helps to overcome drug resistance. Hajipour et al. (2021) modified TiO₂ NPs with CuO. It was reported that CuO modification greatly enhanced the antibacterial characteristics of TiO₂ NPs against Gram-positive *S. aureus* bacteria. The impressive antibacterial response was ascribed to the synergic effects of Cu ion release. Furthermore, the controlled insertion of a foreign element like Ni, Cu, Co, Zn, Se, Mo, Au, ZnO, CuO into the IONPs (known as doping) improves performance and enhances the antimicrobial activity compared to bare IONPs. Depending on particle size, coating materials, and synthesis methods, the antimicrobial activity of doped-IONPs changes. It was also reported that cell absorption and destruction are higher with a smaller size and higher metal molarities. On the other hand, doped IONPs with non-toxic metals (e.g., Ag, Au, Zn, Al) have shown reduced or no toxicity, while toxic heavy metals and metal oxides (e.g., Cr, TiO₂) could increase the toxicity of IONPs, as expected (Tasnim et al., 2023).

Because of their diverse properties, MONPs are very appealing for improving the efficiency of antimicrobial medications in the treatment of antibiotic resistance. Apart from their sole usage, they have also shown their enormous potential in combination with antibiotic drugs because they serve as the drug depot. El-Telbany et al. (2022) reported that ZnO NPs in combination with meropenem improved antibacterial and antibiofilm activity and represented a successful strategy against carbapenem-resistant *P. aeruginosa*. In another study, TiO₂ NPs in combination with nalidixic acid, cephalosporin, β -lactam, and tetracycline showed the potential synergistic activity against methicillin-resistant *S. aureus* (Roy et al., 2010).

Additionally, the potential effects of the synergistic interaction between CuO NPs and anthraquinones were highlighted in increasing the antibacterial activity against *S. aureus* and in reducing live biofilm-forming cells since anthraquinones present antibacterial

and antibiofilm activities (Srivastava et al., 2023). Numerous studies have demonstrated that when antibiotics are complexed with MONPs, their antibacterial efficacy rises (Medic et al., 2024). For instance, in terms of antibiotic conjugates with MONPs, levofloxacin, imipenem, ciprofloxacin, ceftazidime, amoxicillin, oxacillin, azithromycin, cefuroxime, cefotaxime, oxytetracycline, fosfomycin, ofloxacin, norfloxacin, cephalixin, erythromycin, and chloramphenicol were subjected to loading into ZnO NPs (Abdullah et al., 2024). Moreover, MONPs can be engineered to release their antimicrobial agents in a controlled manner, ensuring sustained activity at the infection site. This feature is particularly useful when dealing with biofilms, as it allows them to maintain prolonged exposure to the bacteria within the biofilm matrix, overcoming the resistance conferred by the protective biofilm environment. The influence of characterization parameters on the antimicrobial effect of MONPs was visualized in Figure 4.

Despite the promising potential of MONPs in combating antibiotic resistance, there are several challenges that must be addressed before they can be widely adopted in clinical practice. One of the primary concerns is the toxicity of MONPs, not only to bacteria but also to human cells. While many studies have demonstrated the antibacterial efficacy of MONPs, their effects on human health and the environment remain areas of concern. Prolonged exposure to high concentrations of MONPs could potentially lead to toxicity, causing oxidative stress, inflammation, or even DNA damage in human cells. One of the main challenges for the safe application of MONPs in any biological system is examining the patterns of interaction at the nano-bio interface. The significant degree of diversity and inconsistency in the characterization, assessment, and reporting of experimental data for MONPs is also one of the challenges. Traditional organic synthesis methodologies and NP synthesis and characterization techniques differ greatly. Particularly for biological applications, the techniques for NP standardization and measurements are currently being developed (Kadiyala et al., 2018).

Furthermore, although MONPs seem to be successful against pathogens, many “friendly” bacterial species are seriously threatened when they are exposed to the environment through waste disposal or the food packaging sector. Similarly, due to their wide range of antimicrobial activity, these substances have the potential to seriously disturb the normal human microbiome, which can result in debilitating illnesses, including peptic ulcer disease and *Clostridium difficile* colitis (Kadiyala et al., 2018). Therefore, to mitigate these risks, future research must focus on developing biocompatible and biodegradable MONPs that minimize toxicity while maintaining antimicro-

bial efficacy. This can be achieved through surface modifications, such as coating MONPs with biocompatible materials or optimizing the dosage and delivery methods to ensure that MONPs are delivered only to the site of infection. Additionally, regulatory challenges must be addressed. The approval process for nanoparticle-based therapies is complex, as it requires extensive testing to ensure safety and efficacy. Establishing standardized protocols for the synthesis, characterization, and evaluation of MONPs will be critical in accelerating the clinical translation of these technologies.

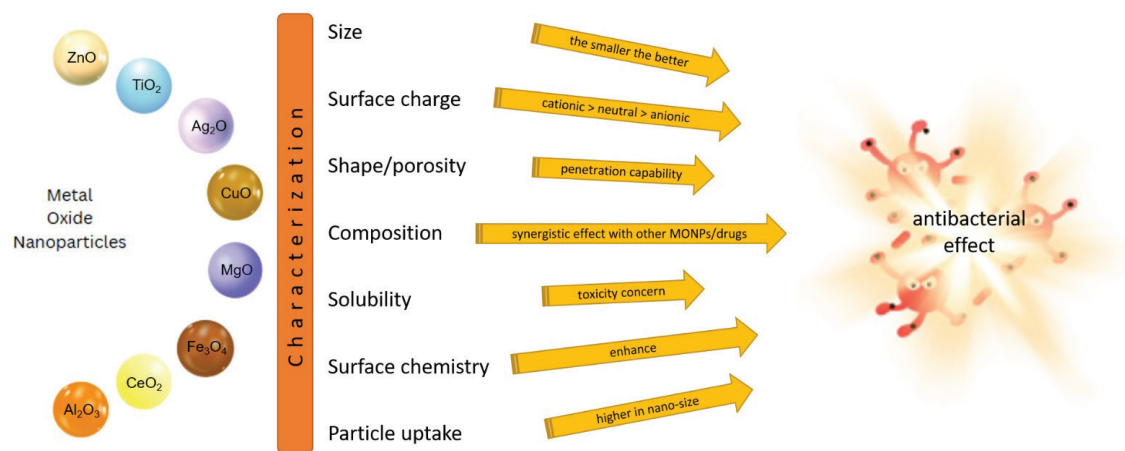


Figure 4. Illustration of the influence of characterization parameters on the antimicrobial effect of MONPs

CONCLUSION

MONPs represent a promising solution to the growing threat of antibiotic resistance. Their unique physicochemical properties, including small size, large surface area, and ability to generate reactive oxygen species, make them effective against a wide range of drug-resistant pathogens, including those that form biofilms. Additionally, their potential as targeted drug delivery systems offers new avenues for improving the efficacy of antimicrobial therapies while minimizing side effects. However, further research is needed to fully understand the long-term effects of MONPs on human health and the environment. Addressing these challenges will be key to realizing the full potential

of these NPs in clinical applications. With continued innovation and collaboration between researchers, clinicians, and regulatory bodies, MONPs could play a crucial role in overcoming the global challenge of antibiotic resistance.

AUTHOR CONTRIBUTION STATEMENT

Conception (GMD, ME), Literature research and writing (GMD, ME, BJ), Reviewing the text (GMD, ME, BJ), Supervision (GMD, ME).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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