Nanoscale Advances

ROYAL SOCIETY OF CHEMISTRY

MINIREVIEW

View Article Online
View Journal

Cite this: DOI: 10.1039/d6na00329j

Antioxidant and antibacterial properties of transition metals and metal oxides for medical uses: mechanisms, design strategies, and biomedical perspectives

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This review provides a critical and integrative analysis of transition metal and metal oxide NPs as emerging multifunctional platforms for biomedical applications, with particular emphasis on their dual antioxidant and antibacterial properties. Beyond conventional descriptive approaches, we systematically correlate physicochemical parameters, including particle size, morphology, surface charge, crystallinity, and functionalization, with biological performance, thereby establishing clear structure–activity relationships governing therapeutic efficacy and biosafety. Key transition metals such as Ag, Cu, Se, Ti, Zn, and Fe, along with their oxides, are examined in terms of their mechanistic pathways, including reactive oxygen species (ROS) modulation, metal ion release, membrane disruption, and enzyme-mimetic antioxidant activity. Recent advances in synthesis strategies, particularly green and bioinspired methods, are highlighted as enabling routes for improving biocompatibility, stability, and targeted functionality. Importantly, this review critically discusses the dual role of ROS in mediating both antibacterial action and oxidative stress regulation, offering a unified framework for designing balanced nano-therapeutics. Comparative analyses reveal that materials with strong antibacterial activity often exhibit weaker intrinsic antioxidant capacity, underscoring the need for rational design of hybrid or multifunctional nanoplatforms. Furthermore, key challenges related to cytotoxicity, long-term biosafety, microbial resistance, and clinical translation are comprehensively evaluated. Strategies such as surface engineering, controlled ion release, and synergistic combinations with conventional antibiotics are proposed to overcome these limitations. By bridging fundamental mechanisms with applied biomedical perspectives, this review provides actionable insights for the next generation of safe, effective, and clinically translatable metal-based nanomaterials.

Received 25th April 2026
Accepted 24th May 2026

DOI: 10.1039/d6na00329j

rsc.li/nanoscale-advances

1 Introduction

The rapid emergence of antibiotic-resistant microorganisms and the increasing prevalence of oxidative stress-related diseases represent major challenges for modern medicine, and create an urgent need for innovative therapeutic strategies. Conventional antimicrobial agents are progressively losing efficacy, prompting the search for alternative therapeutic strategies capable of combating resistant pathogens while minimizing adverse effects.[1–3] Similarly, oxidative stress has been implicated in numerous pathological conditions, including cancer, neurodegenerative disorders, cardiovascular diseases, and chronic inflammation.[4,5] In this context, transition metals and their oxide nanomaterials have emerged as promising candidates for biomedical applications due to their unique physicochemical and catalytic properties including antimicrobial therapy and oxidative stress regulation (see Fig. 1).

Nanotechnology has emerged as a powerful platform for the development of advanced biomedical materials capable of addressing these challenges. In particular, transition metal and metal oxide NPs have demonstrated exceptional potential due to their unique physicochemical characteristics, including high surface-area-to-volume ratio, tunable electronic properties, and catalytic activity.[6,7] Metals such as silver (Ag), copper (Cu), iron (Fe), titanium (Ti), and selenium (Se) exhibit intrinsic antimicrobial and antioxidant properties. When engineered at the nanoscale, these materials display enhanced biological activity resulting from increased surface reactivity and improved interaction with microbial cells.[8,9]

Transition metal NPs and their oxides exert antibacterial effects through multiple mechanisms, including generation of reactive oxygen species (ROS), release of metal ions, disruption of bacterial membranes, interference with cellular

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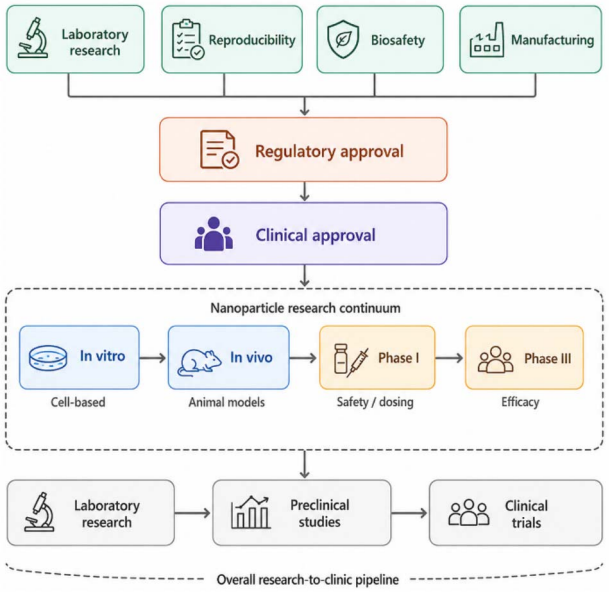

Fig. 1 Overview of transition metal and metal oxide NPs used in biomedical applications.

metabolism.[10] In addition to their antimicrobial effects, several metal-based nanomaterials demonstrate significant antioxidant capabilities by scavenging free radicals, mimicking antioxidant enzymes,[11] and regulating intracellular redox balance.[12,13] Silver (Ag) and its oxide (AgO) have long been recognized for their strong bactericidal properties,[14] while selenium (Se and SeO_2) exhibits potent antioxidant activity through redox cycling and glutathione peroxidase mimicry.[15,16] Copper (Cu and CuO) combines both antibacterial and pro-oxidant properties, useful for wound healing and biofilm inhibition,[17–21] whereas titanium-based materials (Ti, TiO_2) are extensively applied in medical implants with excellent antibacterial coatings and photocatalytic ROS generation.[22,23]

Transition metals possess partially filled d-orbitals that allow them to participate in redox reactions, electron transfer processes, and catalytic transformations. These characteristics enable metal-based nanomaterials to interact with biological systems through mechanisms such as reactive oxygen species (ROS) modulation, metal ion release, and surface catalytic reactions. Consequently, NPs composed of metals such as Ag, Cu, Zn, Fe, Se, Au, and Ti have demonstrated significant antimicrobial and antioxidant activities.[24,25]

In addition to their intrinsic redox properties, the biological performance of these materials strongly depends on several physicochemical parameters, including particle size, morphology, crystallinity, surface charge, and chemical functionalization. NPs typically exhibit higher surface-to-volume ratios compared with bulk materials, which enhances their catalytic activity, ion release, and interaction with microbial membranes. These factors collectively influence both therapeutic efficacy and potential cytotoxicity.[26]

Recent advances in nanotechnology have enabled precise control over nanoparticle synthesis and surface engineering. Techniques such as green synthesis, polymer functionalization, and ligand-mediated targeting allow researchers to design nanomaterials with improved stability, biocompatibility, and therapeutic performance.[27] Furthermore, multifunctional nanoplatforms capable of combining antimicrobial, antioxidant, and drug-delivery functions are increasingly being explored.

Despite these promising developments, several challenges remain before metal-based nanomaterials can be widely implemented in clinical applications. Concerns related to toxicity, long-term stability, bioaccumulation, and environmental impact require careful evaluation. In addition, regulatory approval of nanomaterials for medical use demands rigorous characterization, reproducibility, and biosafety assessment.[28,29]

This review aims to provide a comprehensive overview of transition metal and metal oxide NPs used in biomedical applications, focusing on their antibacterial and antioxidant properties, synthesis strategies, mechanisms of action, toxicity considerations, and future perspectives. We focus on their synthesis strategies, physicochemical properties, mechanisms of antibacterial and antioxidant activity, and emerging biomedical applications. Furthermore, we discuss key challenges related to toxicity, microbial resistance, and clinical translation, and propose future research directions to optimize the balance between efficacy, safety, and sustainability.[30,31]

2 Synthesis strategies for metal and metal oxide NPs

The synthesis method significantly influences nanoparticle structure, stability, and biomedical performance. The Fig. 2 present several physical, chemical, and biological methods have been developed to synthesize metal NPs with controlled size and morphology.

Recent studies focus on green synthesis using plant extracts, biopolymers, and amino acids to enhance biocompatibility and reduce cytotoxicity. Surface functionalization with ligands,

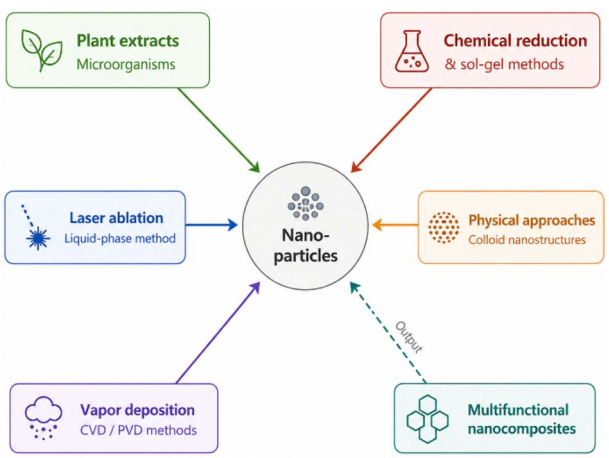

Fig. 2 Common synthesis routes for metal and metal oxide NPs.

polymers, or peptides improves targeting and stability in physiological environments.[32–35]

By leveraging natural resources and advanced functionalization processes, researchers are striving to create safer and more effective materials for medical use, which could significantly benefit drug delivery systems, tissue engineering, and diagnostics.[36–38]

The process of modifying material surfaces with ligands or peptides enhances specific applications, such as targeting tumor cells. Enhanced targeting means more effective delivery of drugs to specific cells, increasing treatment efficiency. Improved stability in physiological conditions ensures that the materials perform consistently in complex biological systems.

The focus on biocompatibility is crucial for advancing medical technologies. As personalized medicine evolves, the need for materials that can safely interact with the human body without causing adverse effects becomes ever more pressing. The advancements cited in the article can lead to enhanced therapeutic options and improved patient outcomes. The incorporation of advanced functionalization techniques allows for innovations in targeted therapies.[39–41] The ability to modify surfaces at the molecular level opens the door to new methodologies in drug delivery where precision is crucial. This could lead to more effective treatments with reduced side effects.[42]

Coupled with innovative surface functionalization techniques, these developments point to a future where medical materials can be optimized for safety and efficiency. As research continues to evolve in this domain, it holds the promise of smarter, environmentally friendly solutions that can transform healthcare delivery and improve patient outcomes.

Various synthesis techniques have been developed to produce metal and metal oxide NPs with controlled size, morphology, and surface characteristics. These approaches can generally be classified into three major categories.[43]

2.1 Chemical synthesis

Chemical reduction methods are widely used for the preparation of metal NPs due to their simplicity and scalability. Reducing agents such as sodium borohydride, hydrazine, and citrate are commonly employed to convert metal ions into metallic NPs. While chemical synthesis provides precise control over particle characteristics, it may involve toxic reagents and generate environmentally hazardous by-products.[44,45]

2.2 Physical synthesis

Physical techniques include laser ablation, evaporation–condensation, vapor deposition and mechanical milling. These methods typically produce highly pure NPs but often require expensive equipment and high energy consumption, limiting large-scale production.[3,4]

2.3 Green synthesis

Green synthesis has emerged as an environmentally friendly alternative that utilizes biological systems such as plant extracts, bacteria, fungi, and algae. Biomolecules present in these systems act as both reducing and stabilizing agents, enabling the formation of NPs without toxic chemicals. Green synthesis approaches offer several advantages reduced environmental impact, improved biocompatibility and lower energy consumption. Nevertheless, challenges remain regarding reproducibility and scalability, which must be addressed before industrial implementation.[5,46]

3 Physicochemical parameters influencing bioactivity

The biological performance of metal NPs is strongly influenced by their physicochemical properties. Parameters such as particle size, morphology, surface charge, crystallinity, and chemical composition determine how NPs interact with biological systems. Overall, rational engineering of nanoparticle physicochemical parameters provides an effective strategy to optimize antimicrobial and antioxidant performance while minimizing adverse biological effects.

3.1 Particle size and surface area

Particle size significantly affects nanoparticle–cell interactions. Smaller NPs possess larger surface area relative to volume, enabling stronger interactions with bacterial membranes and enhanced catalytic activity. NPs smaller than 50 nm typically demonstrate improved antibacterial performance due to their ability to penetrate microbial cell walls and generate reactive oxygen species more efficiently. Smaller NPs possess larger surface-to-volume ratios, which enhance catalytic activity and facilitate interactions with microbial cell membranes.[47]

As a result, nanoscale particles often exhibit significantly higher antimicrobial efficiency compared with their bulk counterparts. However, reduced particle size may also increase cytotoxicity and cellular uptake, potentially leading to undesirable effects in healthy tissues. Therefore, optimizing nanoparticle size is essential to balance therapeutic efficacy and biosafety.[48]

3.2 Morphology and crystal structure

Nanoparticle shape also plays an important role in determining biological activity. Rod-shaped, star-shaped, and sheet-like NPs often exhibit enhanced interactions with microbial membranes compared with spherical particles due to their anisotropic surface structures.[5] The Fig. 3 provide the physicochemical characteristics of NPs, including size, morphology, and surface charge, strongly influence their biological activity. Nanoparticle morphology, including spherical, rod-like, cubic, or flower-like structures, influences their surface reactivity and interaction with biological molecules.

For example, rod-shaped NPs often display enhanced membrane penetration capabilities, whereas highly faceted crystalline structures may expose reactive catalytic sites.[49]

Crystal structure also affects electron transfer processes and redox behavior, which are critical for ROS generation and antioxidant activity. Surface charge influences electrostatic interactions with bacterial cells. Since bacterial membranes are

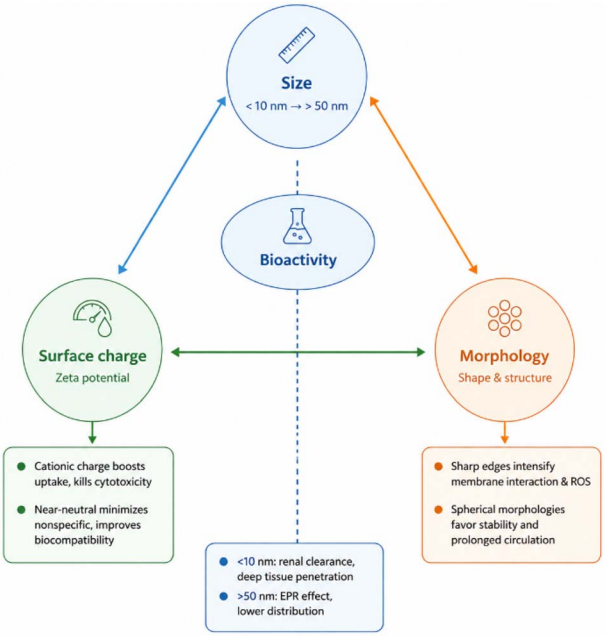

Fig. 3 Influence of nanoparticle size, morphology, and surface properties on biological activity.

typically negatively charged, positively charged NPs display stronger adhesion and improved antibacterial effects.[50]

Morphology and crystal structure also affect biological interactions. For example, rod-shaped NPs often exhibit stronger membrane interactions compared with spherical particles due to anisotropic surface energy distribution. Similarly, crystal facets in materials such as TiO_2 and ZnO can influence photocatalytic ROS production and thus antimicrobial efficiency.[51]

3.3 Surface charge and functionalization

Surface modification strategies such as polymer coating, ligand attachment, or biomolecule conjugation can significantly improve nanoparticle stability and biocompatibility. Examples include PEGylation, chitosan coating and antibody conjugation. These strategies enhance nanoparticle dispersion, reduce aggregation, and enable targeted delivery.[12]

Surface charge plays a key role in nanoparticle–cell interactions. Positively charged NPs tend to interact more strongly with negatively charged bacterial membranes, enhancing antimicrobial activity. Surface functionalization with polymers, peptides, or biomolecules can further improve nanoparticle stability and targeting ability.

Common functionalization strategies include polymer coatings (PEG, chitosan), peptide or antibody conjugation, biomolecule immobilization and ligand-based targeting systems. These modifications can improve biocompatibility, prevent aggregation, and enable targeted drug delivery.

Surface charge plays a crucial role in nanoparticle–cell interactions. Positively charged NPs tend to exhibit stronger antibacterial effects because bacterial membranes are generally negatively charged, promoting electrostatic attraction and membrane disruption.

Surface functionalization with polymers, peptides, or biomolecules can significantly improve nanoparticle stability and targeting ability. Functionalization strategies such as PEGylation, chitosan coating, or antibody conjugation enhance colloidal stability, reduce nonspecific toxicity, and enable targeted delivery to infected tissues.[13]

4 Antibacterial mechanisms of metal and metal oxide NPs

Metal NPs exert antibacterial activity through multiple mechanisms. Metal NPs exert antibacterial activity through multiple mechanisms including ROS generation, membrane disruption, and interference with intracellular processes (see Fig. 4).

4.1 Reactive oxygen species generation

One of the primary mechanisms involves the generation of reactive oxygen species (ROS), including superoxide radicals, hydroxyl radicals and hydrogen peroxide.[6] These ROS species damage bacterial membranes, proteins, and nucleic acids. Metal-based NPs exhibit antimicrobial activity through several complementary mechanisms.

Many metal oxide NPs, including TiO_2, ZnO, and CuO, can generate reactive oxygen species under physiological conditions or light irradiation.[7,9,24] ROS such as superoxide radicals, hydroxyl radicals, and hydrogen peroxide cause oxidative damage to bacterial membranes, proteins, and DNA. The antioxidant activity of NPs involves several ROS scavenging pathways (see Fig. 5).

4.2 Membrane disruption

Direct physical interaction between NPs and bacterial membranes can lead to structural damage, increased permeability, and leakage of intracellular components.[26] Metal NPs

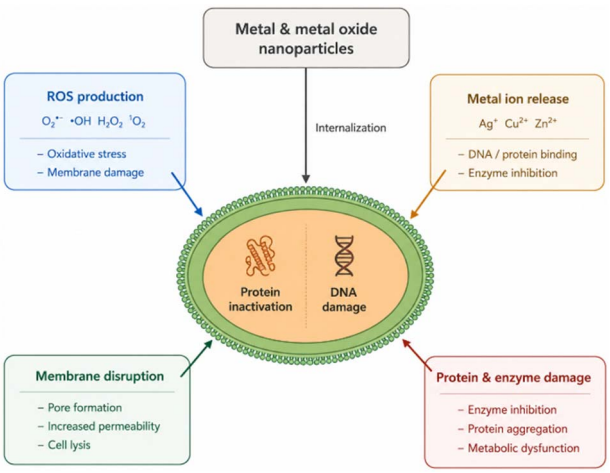

Fig. 4 Schematic representation of antibacterial mechanisms of metal NPs.

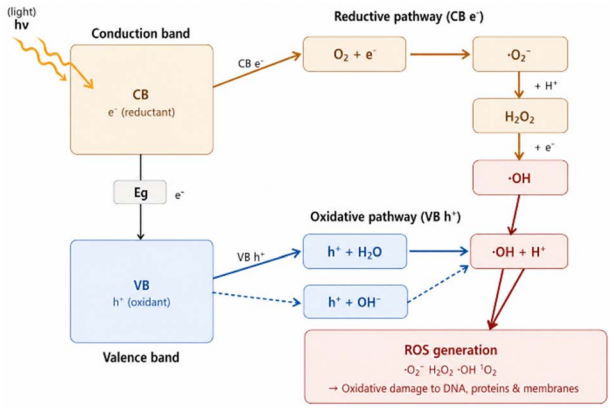

Fig. 5 ROS scavenging pathways in nanoparticle antioxidant activity.

can directly interact with bacterial membranes, leading to membrane permeability changes, leakage of cellular components and structural damage. As can be see Fig. 6, NPs can penetrate biofilms and disrupt microbial communication and metabolic pathways.[27]

4.3 Metal ion release

Metal ions released from NPs, including Ag^{+}, Cu^{2+}, and Zn^{2+}, interact with bacterial enzymes and nucleic acids. These ions disrupt metabolic pathways, inhibit enzyme activity, and interfere with DNA replication.[25,48]

4.4 DNA and protein damage

Metal ions and NPs may bind to thiol groups in proteins and nucleic acids, leading to enzyme inactivation and inhibition of cellular functions. The combination of these mechanisms makes metal-based NPs highly effective antimicrobial agents with reduced susceptibility to traditional resistance pathways.[30]

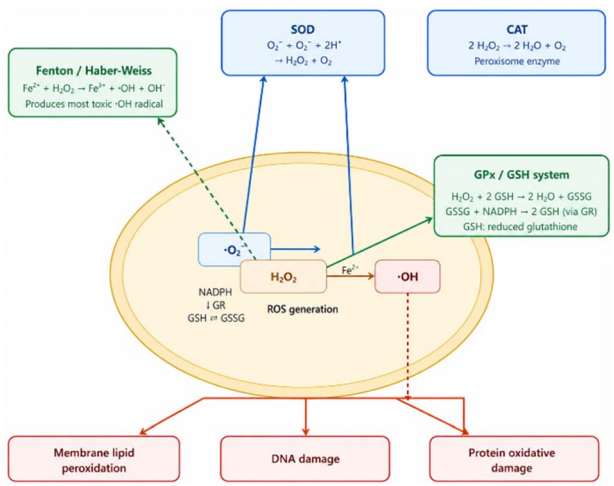

Fig. 6 Interaction of NPs with bacterial biofilms.

5 Antioxidant mechanisms

In addition to antimicrobial activity, several metal oxide NPs exhibit antioxidant properties. CeO_2 NPs are particularly notable due to their ability to cycle between Ce^{3+} and Ce^{4+} oxidation states. This redox cycling allows them to mimic natural antioxidant enzymes such as superoxide dismutase and catalase, enabling efficient scavenging of reactive oxygen species.[8] Similarly, ZnO and Fe_3O_4 NPs can modulate oxidative stress through catalytic reactions that neutralize free radicals. These properties make them attractive candidates for treating diseases associated with oxidative damage. Some metal oxide NPs exhibit enzyme-like antioxidant properties capable of scavenging reactive oxygen species (see Fig. 7).

5.1 Free radical scavenging

Certain NPs neutralize reactive oxygen species by donating electrons or hydrogen atoms.[6]

5.2 Enzyme-mimetic activity

Some NPs mimic natural antioxidant enzymes such as superoxide dismutase, catalase, and peroxidase.[31]

5.3 Redox cycling

Metals such as selenium participate in redox cycling reactions that help maintain cellular redox balance.[42]

6 Comparative properties of metal NPs

To better illustrate the diversity and biomedical potential of transition metal and metal oxide NPs, a comparative overview of their physicochemical characteristics and biological activities is presented in Table 1.

These nanomaterials exhibit distinct properties depending on their chemical composition, particle size, morphology, and surface characteristics, which collectively influence their

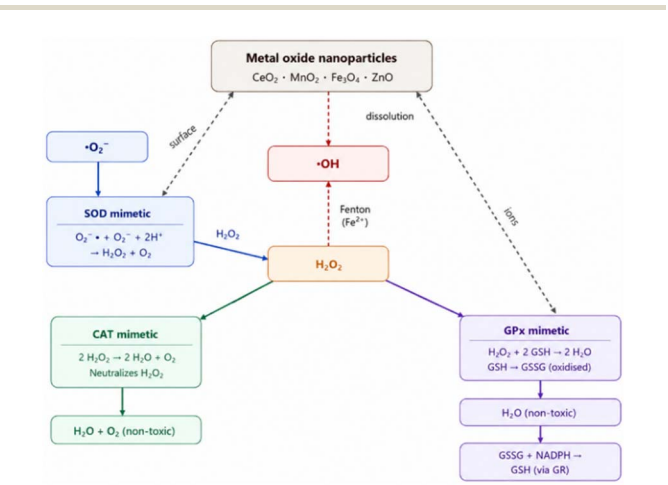

Fig. 7 Antioxidant mechanisms of metal NPs.

Table 1 Comparative physicochemical properties and biomedical activities of transition metal and metal oxide NPs

NPs	Size (nm)	Properties	Antibacterial mechanism	Antioxidant mechanism	Biomedical applications	Limitations
Ag	5–100	High electrical conductivity, strong ion release (Ag^+), high surface reactivity	Membrane disruption, Ag^+ ion release, ROS generation, DNA interaction	Weak intrinsic antioxidant activity	Wound dressings, antimicrobial coatings, medical devices	Cytotoxicity at high concentrations
ZnO	10–200	Wide band gap semiconductor, strong photocatalytic activity	ROS production, Zn^{2+} ion release, membrane penetration	Moderate radical scavenging	Antibacterial coatings, drug delivery, biosensors	Phototoxicity under UV
CuO	10–150	Redox-active surface, Fenton-like catalytic activity	ROS generation, lipid peroxidation, Cu^{2+} ion release	Moderate antioxidant properties	Antimicrobial surfaces, wound healing	Potential oxidative cytotoxicity
TiO_2	10–200	Photocatalytic semiconductor, high chemical stability	ROS generation under UV/visible light, membrane damage	ROS modulation under controlled conditions	Implant coatings, photodynamic therapy	Limited activity without light
CeO_2	5–50	Ce^{3+}/Ce^{4+} redox cycling, oxygen vacancy defects	Moderate antibacterial activity *via* membrane interaction	Strong antioxidant (SOD/CAT mimetic activity)	Neuroprotection, anti-inflammatory therapies	Lower direct antimicrobial activity
Fe_3O_4	10–100	Magnetic properties, good biocompatibility	ROS generation under magnetic stimulation	Moderate antioxidant activity	Drug delivery, MRI contrast agents	Limited intrinsic antimicrobial activity
Se	20–150	Redox-active element, high biological compatibility	ROS modulation, metabolic inhibition	Strong antioxidant activity *via* glutathione pathways	Antioxidant therapies, anticancer research	Narrow therapeutic window
Au	5–100	High stability, tunable surface chemistry	Membrane interaction and enzyme inhibition	Limited antioxidant activity unless functionalized	Drug delivery, biosensing, imaging	High cost

interaction with biological systems. In particular, metals such as silver, copper, zinc, iron, and selenium, as well as their corresponding oxides, have demonstrated significant antibacterial and antioxidant capabilities through mechanisms including reactive oxygen species (ROS) generation, membrane disruption, metal ion release, and enzyme-mimetic activity. By summarizing key parameters such as nanoparticle composition, typical size range, dominant mechanisms of action, and representative biomedical applications, this table provides a concise comparison that highlights both the similarities and unique advantages of different metal-based nanomaterials in antimicrobial and antioxidant therapies.

While Table 1 provides a comparative overview of the physicochemical characteristics and general biomedical functions of major transition metal and metal oxide NPs, a deeper understanding of their practical applications also requires examining how these materials are synthesized and engineered. In recent years, significant progress has been made in developing controlled synthesis strategies that allow precise tuning of nanoparticle size, morphology, and surface properties, which are critical parameters governing their biological performance. Consequently, a more detailed comparison of representative nanomaterials reported in recent studies is presented in Table 2, focusing on their synthesis methods, particle size ranges, and experimentally observed antibacterial or antioxidant activities.

To further highlight recent developments in the biomedical application of metal-based nanomaterials, Table 2 summarizes representative transition metal and metal oxide NPs reported in recent studies, with emphasis on their synthesis approaches, particle size ranges, and corresponding biological activities. The synthesis strategy plays a crucial role in determining nanoparticle physicochemical properties such as size distribution, morphology, surface charge, and stability, which in turn influence their interaction with microbial cells and biological environments.

Various preparation methods, including chemical reduction, hydrothermal synthesis, sol–gel processes, co-precipitation, and green synthesis using biological extracts, have been widely employed to produce NPs with tailored characteristics. These engineered nanomaterials have demonstrated promising antibacterial and antioxidant performance against a wide range of microorganisms and oxidative stress models through mechanisms such as reactive oxygen species generation, membrane damage, and catalytic redox activity. The comparative overview provided in Table 2 therefore offers valuable insights into how synthesis methods and structural parameters influence the biomedical functionality of transition metal and metal oxide NPs.

As illustrated in Table 2, the biological performance of metal-based NPs is strongly influenced by their synthesis route and resulting structural characteristics. NPs produced through controlled methods such as hydrothermal synthesis, sol–gel processes, or green synthesis often exhibit enhanced stability and optimized size distributions, which contribute to improved antibacterial and antioxidant efficiency. In particular, smaller NPs generally demonstrate stronger antimicrobial activity due to their larger surface area and enhanced interaction with microbial membranes. Furthermore, certain metal oxide NPs such as CeO_2, ZnO, and TiO_2 display notable catalytic or redox properties that enable both ROS generation for antimicrobial

Table 2 Comparison of representative transition metal and metal oxide NPs used in biomedical applications, highlighting their synthesis approaches, particle size ranges, and dominant antibacterial or antioxidant mechanisms

NPs	Synthesis method	Size (nm)	Target microorganisms	Biological activity	Ref.
Ag	Chemical reduction	10–40	*E. coli*, *S. aureus*	Strong antibacterial activity *via* membrane disruption and ROS generation	26 and 49
CuO	Sol–gel method	20–50	Gram-positive and Gram-negative bacteria	Metal ion release and oxidative stress induction	3 and 51
ZnO	Hydrothermal synthesis	30–80	*E. coli*, *P. aeruginosa*	ROS generation and photocatalytic antibacterial activity	4, 5 and 51
TiO_2	Sol–gel/hydrothermal	15–60	Bacterial biofilms	Photocatalytic ROS production under UV irradiation	7, 43 and 51
Fe_3O_4	Co-precipitation	20–40	Drug delivery systems	Antioxidant enzyme-mimetic activity	5 and 48
Se	Green synthesis (plant extracts)	50–100	Oxidative stress models	Strong antioxidant and radical scavenging activity	5 and 46
Au	Citrate reduction	10–30	Cancer cells/bacterial systems	Antibacterial and biosensing applications	9
Cu	Chemical reduction	30–70	Multidrug-resistant bacteria	ROS generation and protein oxidation	47
MnO_2	Hydrothermal synthesis	40–90	Cellular oxidative stress models	Catalase-like antioxidant activity	6
CeO_2	Precipitation method	5–20	Inflammatory disease models	Redox cycling between Ce^{3+}/Ce^{4+} enabling antioxidant behavior	44

action and ROS scavenging for antioxidant protection. These observations highlight the importance of rational nanoparticle design and synthesis optimization in maximizing the biomedical potential of transition metal nanomaterials.

7 Toxicity, biosafety, and biocompatibility considerations

Despite their promising biomedical applications, transition metal and metal oxide NPs raise important concerns regarding toxicity and long-term biosafety. Their small size and high surface reactivity can lead to unintended interactions with biological systems, potentially inducing oxidative stress, inflammation, and cellular damage.[9] Despite their therapeutic potential, metal-based NPs may present toxicity risks depending on their physicochemical properties. Excessive ROS generation, uncontrolled ion release, and nanoparticle accumulation in tissues can lead to oxidative stress, inflammation, and cellular damage. Strategies to mitigate toxicity include surface functionalization, controlled ion release, targeted delivery systems and biodegradable coatings. Comprehensive toxicity studies, including *in vitro* and *in vivo* models, are essential to ensure safe biomedical applications.[3]

Major toxicity mechanisms include oxidative stress, inflammation, DNA damage and cellular apoptosis. NPs may accumulate in organs such as the liver, spleen, and lungs following systemic administration. To mitigate toxicity risks, researchers have explored several strategies surface functionalization, biodegradable coatings and controlled release systems. Comprehensive *in vivo* studies remain essential for evaluating long-term biosafety. Despite their promising biomedical potential, metal NPs may induce oxidative stress and cytotoxicity depending on their physicochemical properties (see Fig. 8).

One major toxicity mechanism involves excessive generation of reactive oxygen species, which can damage cellular proteins, lipids, and DNA. While ROS production contributes to antibacterial activity, uncontrolled oxidative stress may also affect healthy tissues. Therefore, balancing antimicrobial efficacy with biocompatibility remains a critical challenge.

The biodistribution and clearance of NPs depend on several factors, including size, surface charge, and surface functionalization. NPs smaller than approximately 10 nm may undergo rapid renal clearance, whereas larger particles may accumulate in organs such as the liver, spleen, and lungs through the reticuloendothelial system.[6]

Surface modification strategies have been widely explored to reduce toxicity and improve biocompatibility. For instance, coating NPs with biocompatible polymers such as polyethylene glycol (PEG), chitosan, or proteins can reduce aggregation, enhance stability in physiological environments, and mitigate nonspecific cellular interactions.

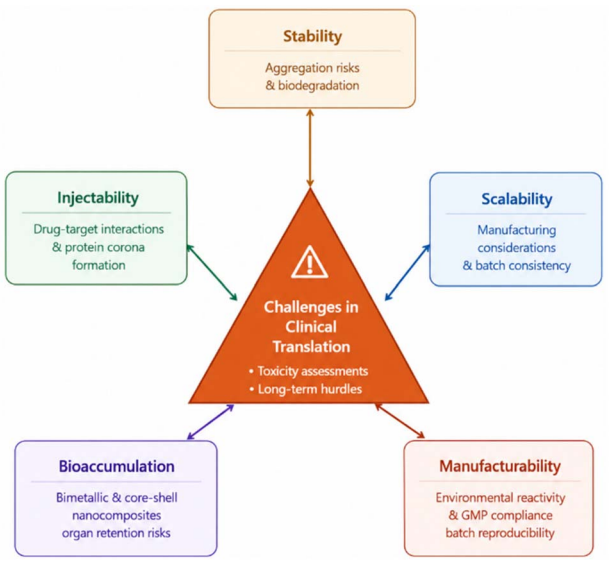

Fig. 8 Cellular toxicity pathways induced by metal NPs.

Furthermore, comprehensive *in vivo* studies remain limited, particularly regarding long-term exposure and potential bioaccumulation. Future research should focus on systematic toxicity assessments, standardized evaluation protocols, and the development of safer nanomaterial designs to facilitate clinical translation.

8 Microbial resistance and synergistic strategies

Although metal-based NPs exhibit broad-spectrum antimicrobial activity, the potential development of microbial resistance remains an important consideration.[29] Unlike conventional antibiotics that typically target specific molecular pathways, metal NPs often act through multiple mechanisms, including ROS generation, metal ion release, and membrane disruption. This multi-target mode of action reduces the likelihood of rapid resistance development.

Nevertheless, adaptive responses in microorganisms have been reported, including increased expression of metal efflux pumps, biofilm formation, and enhanced antioxidant defense systems. Such mechanisms may reduce nanoparticle susceptibility over prolonged exposure.

To mitigate resistance development, several strategies have been proposed. One promising approach involves combining metal NPs with conventional antibiotics, which can produce synergistic antibacterial effects. For example, silver NPs combined with antibiotics such as ampicillin or tetracycline have demonstrated enhanced antibacterial efficacy against resistant bacterial strains.[30,31]

Another strategy involves designing multifunctional NPs incorporating multiple metal components (Ag–Cu or ZnO–TiO_2 composites), which may enhance antimicrobial potency while reducing the required dosage.

Continued research into nanoparticle–microbe interactions is essential to better understand resistance mechanisms and develop more sustainable antimicrobial technologies. Combining NPs with antibiotics or designing multifunctional nanocomposites can reduce the likelihood of resistance and enhance antimicrobial efficacy.

The translation of nanomaterials into clinical applications requires rigorous evaluation of safety, reproducibility, and manufacturing standards. Regulatory agencies require detailed characterization of nanoparticle size distribution, chemical composition, and biological interactions. Challenges include large-scale manufacturing, long-term stability, regulatory approval and cost-effectiveness. Addressing these issues will be essential for successful clinical implementation.

9 Structure–activity relationships in metal-based nanomaterials

Understanding the relationship between nanoparticle structure and biological activity is essential for optimizing therapeutic performance. Structure–activity relationships (SAR) describe how variations in physicochemical properties influence biological interactions (see Fig. 9).

9.1 Particle size: a dual determinant of bioavailability and toxicity

Particle size strongly affects antimicrobial efficiency and cellular uptake. Smaller NPs exhibit greater surface reactivity and enhanced ability to penetrate bacterial cell walls, thereby increasing antibacterial potency. However, excessively small particles may also increase toxicity toward mammalian cells.

Particle size is a primary determinant governing nanoparticle–biological interactions by simultaneously modulating cellular uptake, dissolution kinetics, and ROS generation. Nanoparticles below 20 nm typically exhibit enhanced cellular internalization due to endocytotic uptake pathways and increased surface reactivity. However, this same feature often leads to elevated cytotoxicity associated with uncontrolled ion release and oxidative stress.[52]

In metallic systems such as Ag and Cu nanoparticles, decreasing size significantly accelerates ion dissolution (Ag^+, Cu^{2+}), directly enhancing antimicrobial efficacy but also increasing non-selective toxicity toward mammalian cells.[53] In contrast, metal oxide nanoparticles (*e.g.*, ZnO, TiO_2) exhibit size-dependent modulation of surface defect density and oxygen vacancy concentration, which directly influences photocatalytic ROS production rather than simple ion release. Thus, size regulation represents a trade-off between biological efficacy and biocompatibility, which is strongly material-dependent.[54]

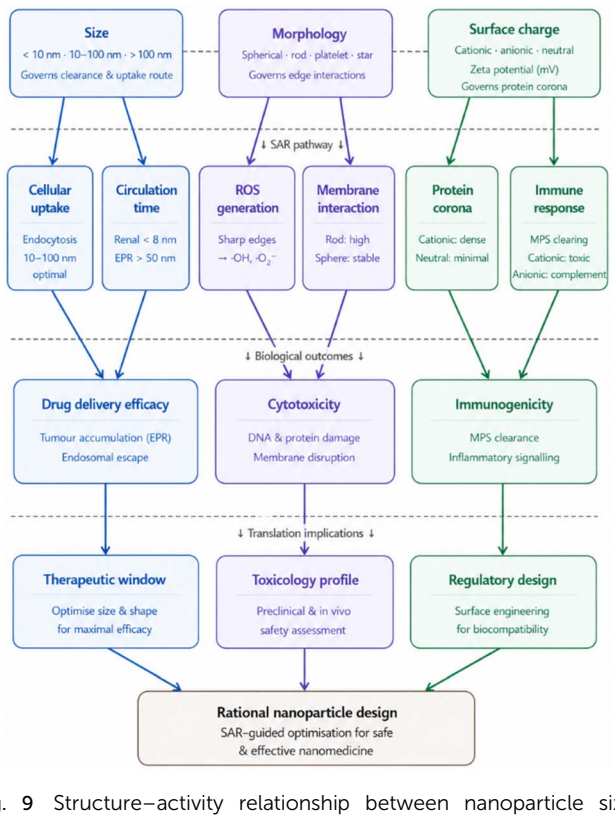

Fig. 9 Structure–activity relationship between nanoparticle size, morphology, surface charge, and biological activity.

9.2 Morphology and crystal facet engineering

Morphology also plays a critical role. Nanorods, nanosheets, and nanostars provide higher surface anisotropy compared with spherical NPs, enabling stronger interactions with microbial membranes and improved catalytic activity. As can be see Fig. 9, the structure–activity relationships provide valuable insights into how nanoparticle physicochemical properties influence antibacterial and antioxidant performance.[55]

Nanoparticle morphology governs the availability of active surface sites and the spatial distribution of reactive crystal facets. Anisotropic structures such as rods, stars, and plates exhibit higher antibacterial activity compared to spherical counterparts due to enhanced membrane contact points and localized electric field intensification at sharp edges. For example, ZnO nanorods and TiO_2 nanoplates expose high-energy facets that favor electron transfer reactions and ROS generation under physiological or photoactivated conditions. Conversely, spherical nanoparticles tend to be more stable but less reactive due to lower surface defect density. This highlights that morphology does not merely influence geometry but directly dictates catalytic and biological reactivity.[56]

9.3 Surface charge and interfacial biointeractions

Surface charge critically regulates electrostatic interactions with bacterial membranes, which are typically negatively charged due to phospholipid and lipopolysaccharide content. Positively charged nanoparticles demonstrate enhanced bacterial adhesion and membrane disruption, leading to increased antimicrobial activity. However, this same property also promotes rapid opsonization and clearance by the mononuclear phagocyte system (MPS), reducing systemic circulation time. Neutral or PEGylated nanoparticles exhibit improved colloidal stability and reduced protein adsorption but often show weaker direct antimicrobial effects.[57] Therefore, surface charge tuning represents a key parameter controlling the balance between bioactivity and systemic stability.

Surface charge determines electrostatic interactions with biological membranes. Positively charged NPs often demonstrate stronger antibacterial effects due to their enhanced affinity for negatively charged bacterial surfaces. Finally, surface functionalization significantly alters nanoparticle behavior in biological environments. Functional coatings can enhance stability, reduce aggregation, and improve targeting of specific tissues or pathogens.

By systematically tuning these structural parameters, it is possible to design metal-based nanomaterials with optimized antibacterial and antioxidant performance.[58]

9.4 Distinction between metallic and metal oxide nanoparticle systems

A critical distinction must be made between metallic nanoparticles (Ag, Cu, Au) and metal oxide systems (ZnO, TiO_2, CeO_2), as their biological mechanisms fundamentally differ. Metallic nanoparticles primarily exert antimicrobial activity through direct ion release (Ag^+, Cu^{2+}), membrane disruption, and thiol group binding in proteins. In contrast, metal oxides operate *via* ROS generation (photocatalytic or redox-driven), oxygen vacancy-mediated electron transfer, and enzyme-mimetic antioxidant activity (notably CeO_2).[59] For instance, CeO_2 exhibits dual antioxidant/pro-oxidant behavior depending on Ce^{3+}/Ce^{4+} ratio, making its biological response context-dependent, unlike Ag nanoparticles which are predominantly cytotoxic.[60] This mechanistic divergence explains why similar physicochemical parameters may lead to drastically different biological outcomes across material classes.[61]

9.5 Integrated structure–activity framework

Overall, nanoparticle bioactivity cannot be attributed to a single parameter but arises from the interplay between size, morphology, surface charge, and material composition. These parameters collectively determine cellular uptake efficiency, ROS generation pathways, protein corona formation, and dissolution/ion release kinetics.[62] A unified SAR model therefore requires simultaneous consideration of physicochemical and compositional variables rather than isolated descriptors.[63,64]

10 Transition metals in medical applications

10.1 Silver

Silver is a well-known antimicrobial agent, widely used in wound dressings, coatings for medical devices, and topical ointments. The antibacterial mechanism is disruption of bacterial cell membranes, interaction with thiol groups in enzymes and DNA, and induction of ROS generation leading to oxidative stress. For the applications, silver NPs (Ag NPs) in wound healing and burn treatment and Ag-coated catheters to prevent hospital-acquired infections.[14,33,65]

The SEM micrographs (Fig. S1) reveal pronounced, concentration-dependent alterations in the morphology of *E. coli* and *P. aeruginosa* following Ag NPs exposure. In the untreated controls, both bacterial species display intact cell walls with smooth surfaces and well-defined shapes, characteristic of healthy cells. Upon treatment with 50 μg mL^{-1} Ag NPs, early signs of structural stress become apparent, including surface roughening, localized depressions, and partial deformation of the bacterial envelope.

At the higher concentration of 100 μg mL^{-1}, severe cell damage is evident in both strains. Cells appear collapsed, wrinkled, and fragmented, with clear signs of membrane rupture (highlighted by green arrows), leading to leakage of intracellular contents and the presence of cellular debris. Aggregates of Ag NPs are visible in close association with damaged cells, suggesting strong nanoparticle adhesion to the bacterial surface. These morphological disruptions are consistent with a mechanism involving direct physical interaction of Ag NPs with the cell membrane, destabilization of the cell wall, and potential induction of oxidative stress through reactive oxygen species (ROS) generation, ultimately resulting in cell death.

10.2 Selenium

Selenium is an essential trace element involved in antioxidant defense and immune regulation. The antioxidant mechanism are acts as a cofactor in glutathione peroxidase, neutralizes hydrogen peroxide and lipid peroxides, and modulates ROS production in cells. For the applications, selenium NPs (Se NPs) for oxidative stress-related diseases and selenium-based coatings to improve implant biocompatibility.[34] The antibacterial activity of Se NPs was evaluated against *Escherichia coli*, *Bacillus cereus*, and *Staphylococcus aureus* at three different concentrations (50, 75, and 100 μL). The inhibition zone diameters increased with increasing nanoparticle concentration for all tested strains, indicating a clear dose-dependent antibacterial effect (see Fig. 10).

At the lowest concentration tested (50 μL), *S. aureus* exhibited the largest inhibition zone (37 mm), followed by *B. cereus* (13 mm) and *E. coli* (11 mm). This suggests that Gram-positive *S. aureus* is the most susceptible to Se NPs, while Gram-negative *E. coli* is the least sensitive at this concentration.

At 75 μL, inhibition zones increased to 46 mm (*S. aureus*), 24 mm (*B. cereus*), and 19 mm (*E. coli*). The increase in inhibition zone size was more pronounced for *B. cereus* and *E. coli*, indicating enhanced efficacy with higher Se NPs concentrations.

At the highest concentration tested (100 μL), *S. aureus* maintained the highest inhibition zone (51 mm), followed by *B. cereus* (33 mm) and *E. coli* (25 mm). The results confirm that Se NPs exhibit strong antibacterial properties, with greater efficacy against Gram-positive bacteria compared to Gram-negative strains, likely due to differences in cell wall structure and permeability.

In summary, Se NPs demonstrate significant dose-dependent antibacterial activity, with *S. aureus* being the most sensitive strain. These findings support the potential application of Se NPs as effective antimicrobial agents, particularly against Gram-positive pathogens.

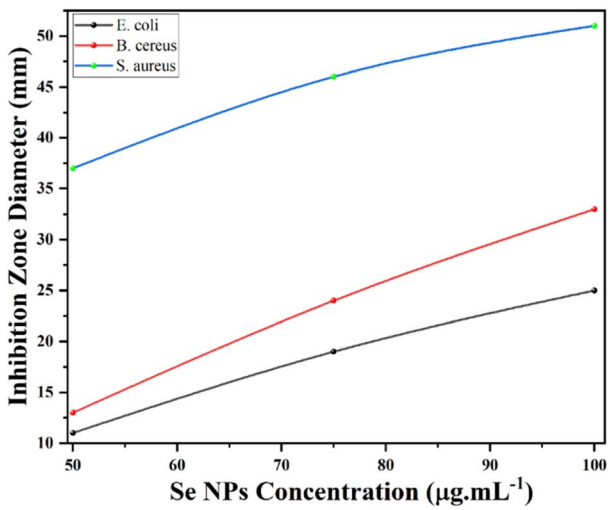

Fig. 10 MICs of Se NPs and against bacterial pathogens.

10.3 Copper

Copper exhibits both pro-oxidant and antimicrobial activities, making it suitable for wound care and antimicrobial surfaces. The antibacterial mechanism are catalyzes Fenton-like reactions to generate ROS, and disrupts bacterial membranes *via* direct ion interaction. For the applications, copper NPs for wound healing gels and Cu coatings for antifouling and biofilm prevention in medical devices.[17,18,66]

The SEM analysis provides direct evidence of the antimicrobial activity of Cu NPs against *E. coli*. As can be seen Fig. S2, in the control sample, cells preserved their typical rod-shaped morphology with smooth and intact surfaces, reflecting normal cell wall integrity. However, upon exposure to Cu NPs, the bacterial cells exhibited severe structural alterations, including cell wall deformation, shrinkage, and surface collapse.

These morphological damages strongly suggest that Cu NPs compromise membrane integrity, leading to leakage of intracellular constituents and eventual cell death. Such effects are consistent with the proposed mechanism of Cu NPs antimicrobial activity, involving both physical disruption of the bacterial envelope and oxidative stress-mediated cytotoxicity.

10.4 Titanium

Titanium is extensively used in orthopaedic and dental implants due to its excellent biocompatibility and corrosion resistance. The antibacterial mechanism are photocatalytic generation of ROS by TiO_2 under UV or visible light and surface modification with TiO_2 nanotubes enhances bactericidal activity. For the applications, Titanium-based implants with antibacterial and Osseo integrative coatings and TiO_2 NPs in photodynamic antimicrobial therapy.[22,67]

The antibacterial activity of TiO_2 NPs combined with amoxicillin was evaluated against *E. coli* and *S. aureus*, as shown in Fig. 11.

The results reveal that the inhibition zone diameter increases with the concentration of TiO_2 NPs, confirming a dose-dependent antibacterial effect.

At 400 μg mL^{-1}, the inhibition zones were 10.3 mm for *E. coli* and 11.3 mm for *S. aureus*. When the concentration increased to 600 μg mL^{-1}, the inhibition zones expanded to 11.3 mm (*E. coli*) and 12.6 mm (*S. aureus*). At the highest tested concentration (1000 μg mL^{-1}), *E. coli* reached an inhibition zone of 11.6 mm, while *S. aureus* showed the maximum inhibition zone of 13.3 mm. These findings demonstrate that TiO_2 NPs exhibit higher antibacterial activity against Gram-positive *S. aureus* compared to Gram-negative *E. coli*. This difference can be attributed to structural variations in bacterial cell walls; the thick peptidoglycan layer of *S. aureus* is more susceptible to disruption by ROS generated by TiO_2 NPs, while the outer lipopolysaccharide barrier in *E. coli* offers partial protection.

Overall, the synergistic effect of TiO_2 NPs with amoxicillin significantly enhances antibacterial performance in a concentration-dependent manner, with greater efficacy observed against *S. aureus*.

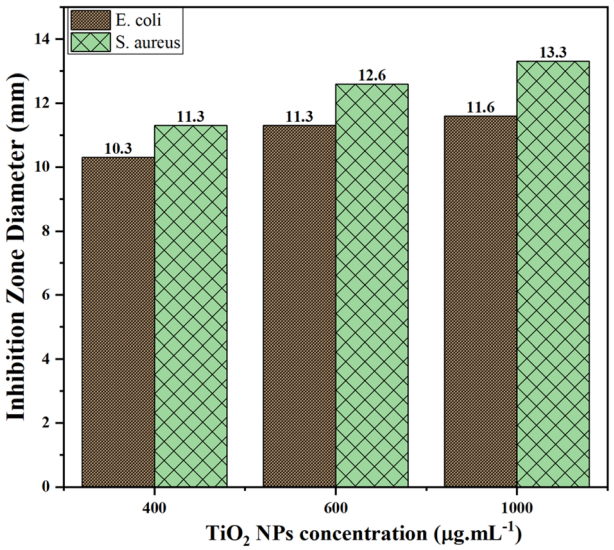

Fig. 11 The antibacterial activity of TiO_2 NPs with amoxicillin against *E. coli,* and (B) *S. aureus*.

11 Metal oxides for antioxidant and antibacterial activities

Metal oxides provide improved stability, controlled ion release, and tunable surface properties for medical applications such as AgO have a highly effective against Gram-positive and Gram-negative bacteria, often used in slow-release wound dressings. SeO_2 exhibits redox cycling and mimics enzymatic antioxidant pathways. CuO induces oxidative stress in bacteria, effective in biofilm disruption. TiO_2 offers ROS generation for antibacterial activity and UV-triggered antioxidant responses.[39,40,68,69]

NPs with high antioxidant activity (CeO_2) tend to have moderate antibacterial properties, whereas those with strong antibacterial activity (Ag_2O, ZnO, CuO) generally exhibit weaker antioxidant effects (see Table 3). This suggests that the biomedical application of metal oxide NPs can be tailored by selecting materials based on the desired therapeutic function whether antioxidant defense, antimicrobial treatment, or dual-purpose hybrid systems.

11.1 Antioxidant activities

NPs have gained significant attention in the field of antioxidants due to their unique properties and effectiveness in scavenging free radicals. Among these, CeO_2 NPs are highlighted for their exceptional antioxidant capabilities. This is attributed to their ability to cycle between the Ce^{3+} and Ce^{4+} oxidation states, simulating the function of natural antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT). Consequently, CeO_2 NPs display remarkable radical-scavenging efficiency. ZnO NPs also exhibit strong antioxidant properties, characterized by their high ability to scavenge free radicals and a considerable antioxidant index, making them effective against oxidative stress.

In contrast, TiO_2 and Fe_3O_4 NPs show a moderate antioxidant effect. TiO_2 NPs utilizes photocatalytic mechanisms to modulate ROS, while Fe_3O_4 NPs activate under specific conditions, either chemically or magnetically, to exhibit antioxidant behavior. MgO NPs and CuO NPs present mild to moderate radical scavenging capabilities, with CuO NPs being particularly effective against hydroxyl and superoxide radicals. Ag_2O NPs demonstrate weak intrinsic antioxidant activity; however, their effectiveness can be improved through techniques such as doping or surface modification. Overall, the wide-ranging antioxidant activities of these NPs suggest their potential applications in various biomedical and environmental fields, highlighting the need for further research into optimizing their use for oxidative stress management.

11.2 Antibacterial activities

This study investigates the antibacterial properties of various metal oxide NPs, focusing on their efficacy against a range of bacterial strains, including multidrug-resistant varieties. It highlights that Ag_2O and ZnO NPs stand out as the most potent antibacterial agents, exhibiting broad-spectrum effectiveness. The mechanisms underpinning their antibacterial properties include the generation of ROS, the release of metal ions (silver or zinc), and the inactivation of proteins and enzymes. CuO and MgO NPs are noted for their high antibacterial activity as well, with CuO exhibiting effectiveness against both Gram-negative and Gram-positive bacteria through the induction of oxidative stress and lipid peroxidation. MgO NPs is shown to particularly target Gram-negative bacteria, leveraging electrostatic binding and creating alkaline stress conditions.

TiO_2 NPs are mentioned for their moderate antibacterial efficiency, which can be notably amplified under UV irradiation due to photocatalytic effects leading to increased ROS production. CeO_2 NPs, while demonstrating strong antioxidant properties, have only moderate effectiveness in combating bacteria, primarily functioning better against Gram-positive ones, indicating a need for a balance between their ROS scavenging ability and direct antibacterial action. Finally, Fe_3O_4 NPs are identified as the least effective agents in an unmodified state. Their antibacterial capacity significantly improves when combined with surface functionalization, underscoring the importance of chemical modifications in enhancing the efficacy of NPs.

12 Mechanistic insights

The article explores the complex behavior of ROS in antibacterial applications. It highlights how ROS play a dual role: on one hand, excessive ROS generation enhances the effectiveness of certain antibacterial materials such as TiO_2, ZnO, CuO, and Ag_2O NPs. On the other hand, materials like CeO_2 NPs utilize the ability to scavenge ROS to exhibit antioxidant properties. The article also emphasizes the significance of ion release, particularly for metals like Ag^+, Zn^{2+}, and Cu^{2+}, explaining that these positively charged ions disrupt essential cellular processes and biomolecules in bacteria, contributing to the bacterial inhibition. Additionally, the content points out that surface charge interactions from materials

Table 3 Comparative overview of metal oxide NPs for antioxidant and antibacterial activities

Metal oxide NPs	Antioxidant activity	Antibacterial activity	Mechanism of action	Ref.
TiO_2	Moderate radical scavenging (DPPH, ABTS); photocatalytic ROS modulation	Effective against *E. coli* and *S. aureus*; higher under UV light	ROS generation, disruption of membranes, protein/DNA interactions	70
ZnO	Strong free radical scavenging; high antioxidant index	Broad-spectrum activity; effective against multidrug-resistant bacteria	ROS production, Zn^{2+} ion release, cell wall penetration	70 and 71 72 73
CuO	Hydroxyl and superoxide radical scavenging	Strong activity against *E. coli*, *S. aureus*, *P. aeruginosa*	Lipid peroxidation, Cu^{2+} release, oxidative stress	74 75
CeO_2	Excellent antioxidant (SOD- & CAT-mimetic activity) *via* Ce^{3+}/Ce^{4+} redox cycling	Moderate antibacterial, more effective on Gram-positive bacteria	ROS scavenging (antioxidant); surface redox and membrane disruption (antibacterial)	76 77 78 79
Fe_3O_4	Moderate radical scavenging capacity	Limited antibacterial activity unless surface-functionalized	ROS generation under chemical/magnetic stimulation	80 81 82
MgO	Mild antioxidant behavior	Strong antibacterial, especially against Gram-negative bacteria	Electrostatic binding, ROS release, alkaline stress	83 84 85 86
Ag_2O	Weak antioxidant capacity; often enhanced when doped	Very strong antibacterial and antifungal action	Ag^+ release, ROS production, protein/enzyme inactivation	74 87 88 89 90

like MgO and CeO_2 NPs also play a role in their antibacterial activity, as do the photocatalytic effects observed in TiO_2 NPs, which enable diverse bioactivities. Overall, this study unpacks the multifaceted mechanisms at play when using materials to combat bacterial infections.

13 Conclusion

Transition metal and metal oxide NPs represent a highly versatile and tunable class of nanomaterials with significant potential to address two major biomedical challenges: microbial resistance and oxidative stress-related diseases. This review demonstrates that their biological performance is not intrinsic alone, but strongly governed by physicochemical parameters such as size, morphology, surface charge, and functionalization, which collectively define their interaction with biological systems. Establishing clear structure–activity relationships is therefore essential for the rational design of next-generation nanotherapeutics.

A key insight emerging from this work is the dual and sometimes competing role of reactive oxygen species (ROS). While, enhanced ROS generation underpins strong antibacterial activity, controlled ROS scavenging is critical for antioxidant and cytoprotective functions. This inherent trade-off highlights the importance of engineering multifunctional or hybrid nanomaterials capable of achieving a precise balance between antimicrobial efficacy and biocompatibility.

Significant progress has been made in developing advanced synthesis and surface engineering strategies, particularly green synthesis and biofunctionalization approaches, which improve safety profiles and environmental sustainability. However, major challenges remain, including nanoparticle-induced toxicity, bioaccumulation, variability in biological responses, and the lack of standardized evaluation protocols. In addition, the potential emergence of microbial resistance to metal-based nanomaterials necessitates the development of synergistic strategies, such as nanoparticle–antibiotic combinations and multi-metal systems.

Future research should prioritize the systematic *in vivo* and long-term toxicity studies, a scalable and reproducible synthesis methods, a smart, stimuli-responsive and targeted nanoplatforms, and a rigorous regulatory framework to facilitate clinical translation. Integrating nanotechnology with biomedical engineering, materials science, and molecular biology will be essential to unlock the full therapeutic potential of these systems.

Overall, this review provides a comprehensive and forward-looking perspective that not only consolidates current knowledge but also defines strategic directions for the development of safe, efficient, and clinically relevant metal-based nanomaterials in modern medicine.

Author contributions

IAMA and ABA were involved in planning and designing the research study. IAMA designed and conducted the experiments, analysed the data, and drafted the manuscript. ABA created the results, drafted the article, corrected errors, aided in the

manuscript's preparation, and supervised this work. The paper was written by all authors and their contributions were approved before submission.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Supplementary information (SI) is available. See DOI: https://doi.org/10.1039/d6na00329j.

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