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Review Article

A review of the antibacterial properties of zinc oxide nanoparticles: synthesis, mechanism of action, and medical applications

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ABSTRACT

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Zinc oxide nanoparticles (ZnO-NPs) have emerged as one of the leading nanomaterials, demonstrating strong antimicrobial properties and high potential in controlling bacterial infections. ZnO-NPs exert their antibacterial effects through the generation of reactive oxygen species, damage to the cell membrane, and disruption of bacterial DNA and protein functions. Numerous studies have shown that these nanoparticles are effective against a wide range of Gram-positive and Gram-negative bacteria, including antibiotic-resistant strains. The small size, high specific surface area, and ability to penetrate bacterial cell walls are key factors contributing to the efficacy of these nanoparticles. Furthermore, due to their minimal side effects on human cells and high biocompatibility, ZnO-NPs are considered a suitable option for clinical and industrial applications. The applications of these nanoparticles have been extensively reviewed, and potential strategies to enhance their efficiency and safety have been proposed. This study highlights the significant potential of ZnO-NPs to either replace or complement existing methods in combating bacterial infections, offering a novel approach to addressing antibiotic resistance and other challenges. This article reviews the antibacterial mechanisms of ZnO-NPs, examining factors influencing their activity and performance, and their potential applications in medical and industrial fields.

KEYWORD

Zinc oxide, metal nanoparticles, multifunctional nanoparticles, reactive oxygen species, antibacterial agents

I. INTRODUCTION

Nanotechnology has garnered significant global attention in the field of modern materials science and its applications in medicine and other scientific disciplines. Nanoparticles, defined as particles with sizes ranging from 1 to 100 nanometers, have demonstrated their efficacy in treating infectious diseases, including antibiotic-resistant strains, in both in vitro and animal models. Due to their high surface area, nanomaterials exhibit remarkable mechanical, optical, magnetic, and chemical properties. These tiny particles represent a modified version of fundamental elements, achieved through the manipulation of their atomic and molecular characteristics. Research has shown that antibacterial mineral materials often include metal nanoparticles and metal oxide nanoparticles, such as Ag, Au, Cu, TiO_2, and Zinc oxide (ZnO). Among metal oxide nanoparticles, ZnO has found extensive applications due to its optical (1), semiconducting (2), ultraviolet (UV) absorbing (3), and antimicrobial (4) properties (5-8). Zinc (Zn) is an essential element used in medicine, biology, and industry. Adults require 8 to 15 mg of Zn daily, with 5 to 6 mg lost through urine and sweat. Zn is vital for bones, teeth, enzymes, and proteins (9). The use of metallic nanoparticles and their oxides represents a promising approach to combating antibiotic resistance (10). Metal oxide nanoparticles are notable for their catalytic inhibitory activity in antimicrobial compounds. However, their bactericidal mechanisms depend on various factors, such as morphology, composition, and concentration (11). Given the emergence of new bacterial mutations, increasing antibiotic resistance, and the proliferation of pathogenic strains, there is a pressing need for the advancement and development of more effective antibacterial agents. ZnO has always been of interest due to its strong antibacterial properties (12). With the rise of bacterial resistance to conventional antibiotics, there is a growing need for innovative and effective methods to combat bacterial infections. Zinc oxide nanoparticles (ZnO-NPs) have emerged as a promising alternative due to their strong antibacterial properties, high biocompatibility, and relatively low production costs. The exact mechanisms of ZnO-NPs antibacterial effects, as well as the optimization of synthesis techniques to increase efficiency and lower potential toxicity, remain unclear despite the large number of investigations that have been done on their synthesis and applications. This article provides a comprehensive review of ZnO-NPs synthesis methods, analyzes their antibacterial mechanisms, and introduces medical applications while proposing strategies for the effective use of this technology in health and treatment. A deeper understanding of these aspects can pave the way for the development of more effective and safer treatments for bacterial infections.

II. STRUCTURE AND PHYSICOCHEMICAL PROPERTIES OF ZINC OXIDE

All of the human body's tissues contain Zn; however, muscle and bone have the highest concentration (around 85% of the total zinc content) (13). Zn is essential for the proper functioning of numerous macromolecules and enzymes, serving as a coenzyme with catalytic and structural roles. Furthermore, protein subdomains can interact with DNA or other proteins thanks to the special framework that zinc-finger structures offer (14). ZnO is an inorganic compound that typically appears as a white powder and is insoluble in water (15). ZnO exhibits three crystalline structures: wurtzite, zinc-blende, and rock salt, with the latter being rarely observed. Crystalline ZnO has a wurtzite structure with a hexagonal unit cell. Each anion is surrounded by four cations in a tetrahedral arrangement, representing sp^3 covalent bonding and creating an asymmetric structure (16). ZnO-NPs are versatile materials widely used in biosensors, cosmetics, drug delivery, and agriculture due to their optical,

electrical, piezoelectric, and antimicrobial properties. The morphology of ZnO-NPs, such as nanorods (17), nanowires (18), and nanoflowers, depends on the synthesis process (19). Traditional methods for synthesizing ZnO-NPs, including sol-gel, hydrothermal, and mechanochemical processes, are often time-consuming, expensive, and require high temperatures and specialized precursors. These methods also generate significant chemical waste (20). In contrast, green synthesis of nanoparticles utilizes renewable organic extracts from sources such as yeast, bacteria, and plants. This approach avoids the use of toxic chemicals and helps reduce waste (21). Compared to other nanoparticles in the same group, Zn demonstrates higher antibacterial activity against Gram-positive bacteria (9). The synthesis of ZnO-NPs has led to their investigation as a novel antibacterial agent. In addition to strong antibacterial and antifungal properties, these nanoparticles exhibit high catalytic and photochemical activities. Furthermore, ZnO has high optical absorption in the UVA and UVB ranges, making it suitable for antibacterial applications and UV protection in cosmetics (22). ZnO is a wide-bandgap semiconductor (3.37 eV at room temperature) with unique properties such as high transparency, strong luminescence, and excellent electron mobility (23). Despite partial covalent characteristics, ZnO primarily features strong ionic bonding in its Zn-O structure, contributing to superior durability, enhanced selectivity, and greater thermal resistance compared to organic and inorganic materials (4). According to an investigation using scanning electron microscopy and energy dispersive X-ray, ZnO-NPs are mostly made up of Zn (37.5%), oxygen (19.9%), and carbon (42.6%), which is consistent with the green synthesis technique used (24).

III. METHODS FOR SYNTHESIS OF ZINC OXIDE NANOPARTICLES

ZnO-NPs are produced using various physical and chemical methods such as solvent evaporation, sol-gel, physical degradation, interference lithography, vapor condensation, and microemulsion deposition (25, 26). However, chemical methods often employ toxic substances that are hazardous to operators and harmful to the environment, while physical methods require high energy, pressure, and temperature (27). Common toxic compounds used in chemical synthesis include triethylamine (28), oleic acid (29), thioglycerol (30), polyvinyl alcohol (31), and ethylene diamine tetraacetic acid (32). These compounds are typically used as stabilizers or coatings to control nanoparticle size and prevent aggregation. However, residual amounts of these compounds in the final product may introduce toxicity, limiting the biomedical and environmental applications of the nanoparticles (25). Green synthesis of metal and metal oxide nanoparticles using biological methods (particularly plant extracts, microorganisms, and fungi) has emerged as a novel field in nanotechnology, offering a sustainable alternative to chemical and physical approaches (33, 34). Natural sources such as plants, algae, fungi, and non-pathogenic microorganisms (e.g., Lactobacillus bacteria) are used in the biosynthesis of ZnO-NPs. This approach represents an eco-friendly, cost-effective, and green solution that utilizes biological compounds (e.g., enzymes and secondary metabolites) for the safe and sustainable production of nanoparticles with minimal environmental contamination and without hazardous chemicals (32, 35). Plant extracts are more widely used in nanoparticle synthesis than microorganism-based methods due to their bioactive phytomolecules (e.g., flavonoids and terpenoids) and advantages such as high biocompatibility and simple extraction processes (36). Phytochemical studies have shown that key plant-derived compounds and metabolites, including lupeol, oleanolic acid, kaempferol glycosides, quercetin, leucocyanidin, ursolic acid, sitosterol, rutin, anthocyanins, and proanthocyanidins possess antioxidant, antibacterial, antimutagenic, and chemopreventive properties (37). Studies indicate that ZnO-NPs synthesized from plant extracts exhibit superior antibacterial properties compared to conventional drugs in disease treatment (38). In this synthesis, plant

components (roots, leaves, stems, seeds, and fruits) are used because their extracts contain high concentrations of phytochemicals that act as stabilizing and reducing agents. The most common method for preparing ZnO-NPs from leaves or flowers involves washing, sterilization, drying, grinding, adding Milli-Q H_2 O, boiling, filtering, and finally mixing with hydrated zinc nitrate, ZnO, or zinc sulfate (39). Although green synthesis of ZnO-NPs is promising, variability in plant extract composition can lead to heterogeneity in nanoparticle size, shape, and purity. This necessitates precise control of reaction parameters (e.g., metal ion concentration, temperature, pH, and time) to ensure reproducibility (40-43). Recent studies have demonstrated the efficacy of lactic acid bacteria (LAB) in mediating ZnO-NP synthesis (44, 45). Given their ability to synthesize metallic nanoparticles (e.g., Se, Au, and Ag), LAB strains are recognized as efficient cellular factories for metal nanoparticle production. Gram-positive LAB possess thick cell walls composed of peptidoglycan, lipoteichoic acid, collagen, and polysaccharides. Due to their negative electrophoretic mobility, these layers serve as sites for biosorption of metal ions and bioreduction, attracting metal cations to initiate nanoparticle biosynthesis (46, 47). Green production of ZnO-NPs using bacteria such as Lactobacillus and Bacillus has gained attention as a sustainable and eco-friendly alternative to chemical methods. Species like Lactobacillus plantarum and Lactobacillus casei significantly contribute to metal ion reduction and ZnO-NP formation through their bioactive metabolites and enzymes. Studies show these nanoparticles are predominantly spherical (average size: 10–13 nm) and exhibit exceptional antibacterial and antibiofilm properties (48-50). Green synthesis of ZnO-NPs has also been achieved using non-Lactobacillus bacteria (e.g., Bacillus subtilis), enabling tailored control over nanoparticle size and morphology. These nanoparticles are effective in organic pollutant removal and exhibit strong antibacterial activity against Salmonella typhimurium, Escherichia coli, and Staphylococcus aureus (S. aureus) (51). Enzymes produced by non-pathogenic Lactobacillus strains can act as reducing, stabilizing, or capping agents in nanoparticle synthesis (43).

IV. The Effect of Zinc Oxide on Gram-Positive and Gram-Negative Bacteria

ZnO-NPs exhibit effective antimicrobial and anti-biofilm properties, impacting a wide range of Gram-positive and Gram-negative bacteria (52). ZnO-NPs effectively target drug-resistant bacteria, disrupt biofilms, and reduce the virulence of pathogens. They also demonstrate promising antifungal properties, particularly for skin infections (53). During the exponential development phase, ZnO-NPs exhibit potent antibacterial properties against both Gram-positive and Gram-negative bacteria. However, their antibacterial efficacy significantly decreases during the lag and stationary phases of bacterial growth (54). Biologically synthesized ZnO-NPs have demonstrated significantly higher growth inhibition compared to chemically synthesized ZnO-NPs and other conventional antimicrobial agents. ZnO also exhibits notable selectivity, greater durability, and good thermal resistance. These unique properties make ZnO a powerful tool in combating a wide range of microorganisms, including *S. aureus* (55, 56), *Escherichia coli* (57). TiO_2, ZnO, and Ag are used in various fields to regulate microbial proliferation. However, ZnO exhibits greater biocompatibility compared to TiO_2 due to its exceptional photocatalytic efficiency (58). Green-synthesized ZnO-NPs demonstrate antibacterial properties against both Gram-positive and Gram-negative bacteria (59). Typically, Gram-negative bacteria show lower sensitivity to ZnO-NPs compared to Gram-positive bacteria. This increased resistance in Gram-negative bacteria can be attributed to the unique structure of their cell walls, which, unlike Gram-positive bacteria, include an additional outer membrane composed of lipopolysaccharides that reduces their susceptibility (60, 61). ZnO-NPs inhibit the formation of amyloid peptide fibrils, which are essential for bacterial biofilm formation (62). The combination of meropenem and ZnO-NPs reduces the expression of genes associated with

biofilm formation. Additionally, the small size of ZnO-NPs enhances their ability to penetrate the biofilm matrix, leading to stronger anti-biofilm activity. Complete biofilm removal in certain areas has been observed using scanning electron microscopy (63). Based on evidence from studies, ZnO-NPs, particularly those synthesized via green methods, are considered promising anti-biofilm agents for medical applications (e.g., implant coatings) and the control of biofilm-related infections (64). According to studies, ZnO-NPs reduce the ability of *S. aureus* to form biofilms by inhibiting the expression of biofilm-related genes such as *ica A*, *ica D*, and *fnb A*. These nanoparticles exhibit strong antibacterial activity against multidrug-resistant strains of *S. aureus*, including methicillin-resistant, vancomycin-resistant, and linezolid-resistant strains (65) (Table 1).

Name of bacteria	Type of bacteria	Effect of ZnO-NPs	Mechanism of action	Reference
Staphylococcus aureus	Gram positive	Inhibition of bacterial growth, damage to the cell wall, and plasma membrane	Production of reactive oxygen species (ROS), disruption of cell membrane function	(66)
		Reduction of biofilm formation	Inhibition of the expression of biofilm-related genes such as *icaA* and *fnbA*	(67)
Streptococcus pyogenes	Gram positive	Increase in cell membrane permeability	Damage to lipids and membrane proteins	(68)
Escherichia coli	Gram negative	Inhibition of bacterial growth, damage to the outer and plasma membranes	ROS production, damage to lipopolysaccharides, and membrane proteins	(69)
Pseudomonas aeruginosa	Gram negative	Reduction of biofilm formation	Disruption of the biofilm matrix and inhibition of bacterial attachment to surfaces	(70)
Klebsiella pneumoniae	Gram negative	Increase the sensitivity to antibiotics	Increase the permeability of the outer membrane and facilitate the entry of antibiotics.	(71)
Bacillus subtilis	Gram positive	Inhibition of bacterial growth and reduction of spore formation	ROS production, damage to the cell membrane, and disruption of DNA function	(25)
Salmonella typhi	Gram negative	Inhibition of bacterial growth and reduction of biofilm formation	ROS production, damage to the outer membrane, and disruption of DNA function	(72)

V. The Effect of Zinc Oxide on Other Microorganisms

ZnO-NPs exhibit strong antifungal and anti-yeast properties against various harmful fungi and yeasts. Studies have shown that biosynthesized ZnO-NPs are effective against *Fusarium solani*, *Fusarium oxysporum*, *Sclerotinia sclerotiorum*, and *Aspergillus terreus* (73). Additionally, ZnO-NPs produced using *Serratia nematodiphila* have shown significant antifungal activity against *Alternaria* species and *Xanthomonas oryzae* pv. *Oryzae* (74). ZnO-NPs significantly inhibit the growth of yeasts such as *Saccharomyces cerevisiae* (75), *Candida albicans* (76), and *Candida tropicalis* (77). Aquatic ecosystems

may be significantly affected by the toxicity of nanoparticles, and algae are an ideal organism for understanding the impact of nanoparticle toxicity. ZnO-NPs have an effect on the algae *Chlorella vulgaris* (78), *Microcystis aeruginosa* (79), and *Spirulina platensis* (80).

VI. Mechanism of Action of Zinc Oxide on Bacteria

ZnO-NPs, recognized as Generally Recognized as Safe by the U.S. Food and Drug Administration (FDA), are a suitable alternative to antibiotics against drug-resistant bacteria (81). ZnO-NPs exert their antibacterial effects by disrupting bacterial DNA replication processes, causing cell membrane rupture, binding to proteins and DNA, generating reactive oxygen species (ROS), and altering (often reducing) the expression of several genes (10). Metal oxide nanoparticles induce oxidative stress, membrane damage, and cell death by infecting bacteria, increasing ROS production, causing membrane peroxidation, lipid bilayer peroxidation, and leakage of cytoplasmic components (82). Due to its powerful oxidative properties, ZnO damages bacterial cell membranes and disrupts their metabolic pathways by generating ROS and releasing zinc ions (Zn^{2+}). Further studies on the antibacterial mechanisms of ZnO-NPs could enhance our understanding of bacterial resistance mechanisms and improve the contact time and efficacy of ZnO-NPs in inhibiting bacteria (11). The reduction of Zn^{2+} disrupts intracellular Zn^{2+} balance, leading to enzyme inactivation, chromatin structure alteration, inhibition of DNA replication, and ultimately bacterial death (83).

A. Generation of Reactive Oxygen Species by Zinc Oxide

The toxicity of metallic and metal oxide nanoparticles is primarily attributed to their ability to generate ROS (84). Several investigations have demonstrated that the high amounts of ROS generated in ZnO aqueous solutions aid in the antibacterial activity of ZnO. These species include hydroxyl radicals (OH), hydrogen peroxide (H_2O_2), and singlet oxygen, which play a key role in killing bacteria (55). ROS disrupt or alter respiratory cycles, protein synthesis, food metabolism, and DNA replication, leading to cell death (25). Exposure to UV radiation stimulates valence band electrons in ZnO-NPs, creating holes in the conduction band that require energy absorption to cross the bandgap (85). Electrons in the conduction band can reduce molecular oxygen on the ZnO surface, forming superoxide anions, which can react with each other to produce other ROS, such as H_2O_2 (86). H_2O_2 penetrates the cell membrane, causing membrane damage and degradation of DNA and membrane proteins. Negatively charged peroxides cannot cross the cell membrane, and OH^- accumulates on the bacterial cell membrane, destroying it (87).

B. Release of Zn^{2+} Ions and Their Impact on the Antibacterial Activity of Zinc Oxide Nanoparticles

The antibacterial activity of ZnO-NPs is primarily associated with the release of Zn^{2+} ions, which can inhibit bacterial growth by disrupting metal-dependent enzymes and osmotic homeostasis. This toxicity occurs even without direct physical contact with the nanoparticles and is highly dependent on environmental conditions, such as soluble compounds and surface defects of the particles (88). ZnO-NPs can slowly release Zn^{2+} ions in aqueous solutions, which can penetrate the cell membrane, leading to protein denaturation and disruption of cellular respiration. However, studies have shown that increasing Zn^{2+} concentration does not significantly enhance antibacterial effects. Additionally, experiments have demonstrated that minimal Zn^{2+} release under certain conditions does not fully explain high cell mortality. Therefore, Zn^{2+} release should not be considered the primary mechanism of ZnO's antibacterial activity (87) (Figure 1).

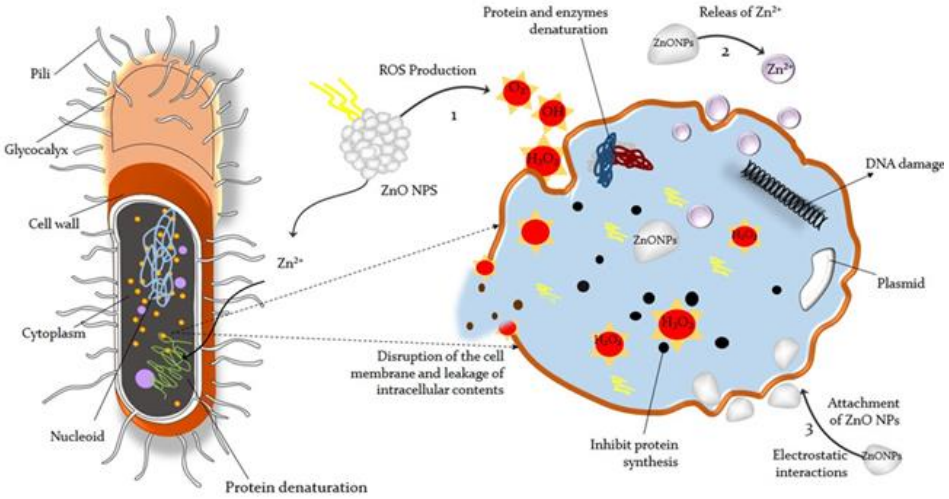

Figure 1. Mechanisms of action of ZnO-NPs on bacteria, including the generation of reactive oxygen species, release of Zn^{2+} ions, and their effects on the cell membrane and bacterial metabolism.

VII. Applications of Zinc Oxide in Medicine and Industry

ZnO nanostructures, due to their multifunctional properties, are utilized in sensors, energy harvesting, and electronic devices. Additionally, in the medical and antiviral fields, ZnO is highly regarded for its excellent biocompatibility, solubility in alkaline environments, and polar surfaces (89). The use of nanoparticles as drug carriers and for targeted delivery of substances, particularly in treating infections caused by microbial biofilms, is a significant and actively researched area among scientists (90). Drug delivery systems are innovative technologies that facilitate the transport of drugs, including tablets and vaccines, into or throughout the body. These systems protect drugs from degradation and maintain their stability until they reach the target site, thereby enhancing the efficacy and safety of therapeutic treatments (91). The small size of nanoparticles enables them to cross the blood-brain barrier (92). Doping ZnO with Gd^{3+} and Al^{3+} improves electrical conductivity and increases charge carrier concentration. The high exciton binding energy of ZnO is attributed to its high dielectric constant, which is influenced by defects such as Zn interstitials and oxygen vacancies. The enhanced dielectric properties of ZnO-NPs are due to oxygen vacancies, nanoscale size effects, and the electronegativity of added impurities. For instance, Li-In doped ZnO achieved a dielectric constant of 3800, with ε′ stabilizing at higher frequencies for doped samples, unlike pure ZnO, where dielectric relaxation was observed in all samples (93). ZnO is well-known for its antibacterial properties in skincare creams and UV protection. The use of modified ZnO-NPs (4%) in coatings for hospital implants can be more effective in controlling bacterial infections. Moreover, these modified nanoparticles are a better option for use in skin lotions and UV protection compared to conventional ZnO (4). In addition to FDA approval, ZnO-NPs are suitable for various biomedical applications, including medical devices, biomedical diagnostics, tissue engineering, healthcare, and drug delivery, due to their simple, safe, and cost-effective production process (94-97). In biology and medicine, ZnO-NPs hold significant value due to their anticancer (98), antimicrobial (99), anti-inflammatory (100, 101), wound-healing (102), bioimaging (103, 104), and antidiabetic (105, 106) properties. The freeze-dry technique was used to create a composite bandage composed of ZnO-NPs and alginate hydrogel. This porous bandage not only demonstrated exceptional antibacterial activity against a wide range of pathogens but also promoted controlled

degradation and accelerated blood clotting (107). According to preliminary research, ZnO-NPs at low concentrations in a biomaterial can enhance tissue integration by improving fibroblast attachment, promoting new blood vessel growth, and accelerating wound healing. ZnO-NPs may also increase levels of angiogenic factors such as vascular endothelial growth factor through the production of ROS (108). Skin wounds should be treated with topical medications that stimulate tissue repair while minimizing free radical production (109, 110). Consequently, having a wound dressing material that possesses both antibacterial properties and wound-healing capabilities is crucial (111).

VIII. Key Challenges in Antimicrobial and Environmental Applications of Zinc Oxide Nanoparticles

Organic materials reduce the antimicrobial efficacy of ZnO-NPs by affecting their stability and surface properties. For instance, ZnO-NPs perform better in organic-free environments because organic compounds limit their activity by coating the nanoparticle surfaces (112). The production process of ZnO-NPs, including the high-energy ball milling of metal powders, reduces particle size and ultimately yields nanoparticles. However, the resulting nanoparticles often have irregular sizes and shapes, which may lead to contamination from the surrounding environment or milling process, rendering them unusable (113). While antimicrobial nanoparticles hold significant potential, they face challenges such as resistance development, biocompatibility and toxicity concerns, environmental impact, nonspecific effects on microbiota, formulation optimization, drug delivery hurdles, and regulatory frameworks (114). The use of man-made nanoparticles in agriculture, such as nanofertilizers and nanopesticides, has led to their accumulation in soil. Although ZnO-NPs are more biocompatible, their antimicrobial properties may disrupt soil microbiota and interfere with key processes such as the nitrogen cycle and plant growth (115). The toxicity of nanoparticles varies depending on their type and concentration. For example, while ZnO-NPs provide UV protection, they can penetrate the skin and generate ROS, leading to cellular damage. Toxicity tests that examine nanoparticle characteristics, exposure pathways, distribution, and biological interactions are essential to ensure safe usage (116). Although the application of ZnO-NPs has been limited due to concerns over toxicity, stability, and environmental effects, targeted synthesis techniques have enabled the development of safer and more efficient formulations. These advancements pave the way for maximizing the antimicrobial and protective capabilities of nanoparticles in healthcare products, provided that safety assessments and regulatory standards evolve alongside technological progress to ensure safer and more effective products (117).

IX. Conclusion

ZnO-NPs have garnered significant attention due to their unique properties, such as antimicrobial and optical activities. As potent antibacterial agents, ZnO-NPs exhibit broad applications, particularly in combating antibiotic-resistant bacteria. By penetrating bacterial cell membranes, ZnO-NPs disrupt membrane integrity and reduce the transcription of genes associated with oxidative stress resistance. In the medical field, these nanoparticles are utilized in drug delivery, bioimaging, cancer therapy, and wound healing. Green synthesis of ZnO-NPs using natural resources offers an environmentally friendly and cost-effective approach. Key challenges in biosynthesis include heterogeneity in nanoparticle size and shape, toxicity arising from ROS and Zn^{2+} ions, environmental accumulation, and scalability issues in large-scale production. However, owing to their high biocompatibility and safety, ZnO-NPs are regarded as promising alternatives to antibiotics and are increasingly being explored for advanced industrial and biomedical applications.

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