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# Green Synthesis of Zinc Oxide Nanoparticles: Preparation, Characterization, and Biomedical Applications - A Review

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**Abstract:** Over the last decade, biomedical nanomaterials have garnered significant attention due to their remarkable biological properties and diverse applications in biomedicine. Metal oxide nanoparticles (NPs) are particularly notable for their wide range of medicinal uses, including antibacterial, anticancer, biosensing, cell imaging, and drug/gene delivery. Among these, zinc oxide (ZnO) NPs stand out for their versatility and effectiveness. Recently, ZnO NPs have become a primary material in various sectors, such as pharmaceutical, cosmetic, antimicrobials, construction, textile, and automotive industries. ZnO NPs can generate reactive oxygen species and induce cellular apoptosis, thus underpinning their potent anticancer and antibacterial properties. To meet the growing demand, numerous synthetic approaches have been developed to produce ZnO NPs. However, traditional manufacturing processes often involve significant economic and environmental costs, prompting a search for more sustainable alternatives. Intriguingly, biological synthesis methods utilizing plants, plant extracts, or microorganisms have emerged as ideal for producing ZnO NPs. These green production techniques offer numerous medicinal, economic, environmental, and health benefits. This review highlights the latest advancements in the green synthesis of ZnO NPs and their biomedical applications, showcasing their potential to revolutionize the field with eco-friendly and cost-effective solutions.

**Keywords:** antimicrobial, antioxidant, green synthesis, nanomedicine, nanoparticle, zinc oxide



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## Introduction

Zinc (Zn) is essential to human, animal, and plant metabolism, playing a key role in muscles, bones, skin, and brain function.[1] As an essential trace mineral, zinc oxide (ZnO) is commonly used in dietary supplements, cosmetics, and medical products. While most commercially available ZnO is synthetically produced, it also naturally occurs in the earth's crust as the mineral zincite. ZnO is known for being safe and gentle on human skin, making it ideal for various topical applications.[1] ZnO nanoparticles (NPs) have diverse applications across multiple industries, including use as photocatalysts,[2] ethanol gas sensors,[1,3] ultraviolet (UV) light-emitting devices,[4,5] and in the pharmaceutical,[6] and cosmetics sectors.[7] Metal and metal oxide NPs, including ZnO NPs are integral to advancements in textiles, medicine, catalysis, pharmaceuticals, agriculture, heavy industrial consumer products, and antimicrobial testing.[8–11] This versatility highlights the significant role of ZnO and its nanoparticulate forms in driving innovation and improving products that touch our daily lives.[9–11]

ZnO NPs offer a unique blend of safety, affordability, and versatility, making them a standout among metal oxide NPs.[12] Their strong UV absorption and transparency to visible light make them highly effective as sunblock agents.[13] In addition, their ability to generate reactive oxygen species (ROS) has spurred research into their antibacterial and anticancer properties.[14] ZnO NPs are increasingly recognized for their biomedical applications, particularly in drug delivery systems and bioimaging.[15] They can target and release drugs at specific sites, enhancing therapeutic outcomes, and their bioimaging capabilities improve the visualization of biological processes and disease states.[13] The United States Food and Drug Administration (FDA) has approved ZnO in bulk as a generally recognized safe substance, and ZnO NPs larger than 100 nm are deemed to be compatible with biological systems,[15] highlighting their potential in pharmaceutical delivery applications. Moreover, ZnO NPs are being explored for wound healing due to their antimicrobial properties and ability to promote tissue regeneration. This multifunctionality positions ZnO NPs as a promising tool in various medical and pharmaceutical applications, driving innovation and improving patient care.[15]

Recent research highlights the advantages of using biological sources as reducing agents in the synthesis of ZnO NPs.[16] This eco-friendly approach is favored for its non-hazardous simplicity, low energy consumption, and cost-effectiveness. Plant-derived compounds, such as terpenoids, alkaloids, polyphenols, saponins, flavanones, and tannins, have been shown to effectively reduce Zn precursors. In addition, plant extracts have demonstrated superior efficacy against bacterial and fungal infections.[17] This review provides a comprehensive overview of the latest advancements in the green synthesis of ZnO NPs and explores their promising medical applications.

## Transition from Conventional to Green Synthesis of ZnO NPs

ZnO NPs offer a balanced combination of low toxicity and high biodegradability compared to other nanomaterials, such as gold nanoparticles (AuNPs), which are non-biodegradable and can accumulate in tissues.[18,19] While liposomes also possess non-toxic and biodegradable characteristics, ZnO NPs provide additional therapeutic benefits due to their antibacterial and anti-inflammatory properties.[20] Moreover, ZnO NPs are multifunctional and can selectively generate ROS in cancer cells, a significant advantage in targeted cancer therapy.[21] Their potential applications in imaging and diagnostics further enhance their appeal.[21]

NPs can be generated through biological, chemical, and physical methods.[22] However, physical methods are not ideal for large-scale production due to low yield, high energy requirements, and increased input costs.[23,24] While chemical methods have become the preferred choice for NP synthesis,[22,23,25] they are time-consuming, labor-intensive, and pose hazardous effects on humans and the environment.[22,23,25] In addition, chemo-synthesized NPs often exhibit instability and toxicity, limiting their biomedical applications.[26,27] Therefore, developing efficient, reliable, safe, and environmentally friendly techniques for NP synthesis is crucial.[27]

Recently, green biological-mediated approaches have gained attention.[28,29] Plants and microorganisms can generate NPs that are safe, environmentally sustainable, and cost-effective.[30,31] Biological agents, such as algae, bacteria, fungi, and plants, can serve as solvents and stabilizers, creating a green synthetic pathway for NPs and reducing the toxicity of the end product.[32] This ability not only diminishes environmental pollution but also transforms heavy metals (HMs) from industrial wastes into safer compounds. The distinctive biochemical mechanisms of these agents offer novel and

untapped avenues for converting inorganic metallic ions into metal NPs.[30,33,34] Plants contain diverse metabolites and biomolecules, including proteins, vitamins, coenzyme-based intermediates, phenols, flavonoids, and carbohydrates, which can interact with metal ions and reduce their sizes to the nano range.[35] For example, flavonoids, characterized by their polyphenolic structures and multiple hydroxyl (-OH) groups attached to aromatic rings, can donate electrons to reduce metal ions such as $Zn^{2+}$ and $Ag^{+}$ to their corresponding metallic NPs. Similarly, phenolic compounds, with their hydroxyl groups, act as electron donors, facilitating the reduction of metal ions.[17,36]

Once the metal ions are reduced, flavonoids and phenolic compounds further contribute to the stabilization and capping of the NPs.[37] The hydroxyl and other functional groups in these compounds form strong interactions, such as hydrogen bonding and van der Waals forces, with the metal surface, preventing NP aggregation and enhancing their stability in suspension.[37,38] This capping process not only stabilizes NPs but also improves their biocompatibility, making them suitable for various biomedical applications.[38]

For instance, the flavonoid quercetin has been shown to effectively synthesize silver nanoparticles (AgNPs).[39] Quercetin, with its multiple hydroxyl groups, reduces $Ag^{+}$ to Ag and subsequently caps the AgNPs, enhancing their stability. Another example involves the use of *Aloe vera* extract in the green synthesis of ZnO NPs.[40] *A. vera* extract, rich in polyphenols, vitamins, enzymes, and amino acids, acts as both a reducing and capping agent. The polyphenolic compounds, such as flavonoids and tannins, reduce $Zn^{2+}$ ions from zinc nitrate to ZnO NPs.[40,41] Simultaneously, the organic molecules, including polysaccharides and proteins in the extract, cap the NPs, preventing aggregation and ensuring stability.[40] This dual action of reduction and capping by *A. vera* extract not only prevents ZnO NPs from clumping together but also enhances their biocompatibility and dispersibility in aqueous solutions, making this method environmentally friendly and suitable for various applications, including antibacterial and anticancer therapies.[41]

Similar to plants, green algae (Chlorophyceae), blue-green algae (Cyanophyceae), brown algae (Phaeophyceae), and red algae (Rhodophyceae) have secondary metabolites and demonstrate remarkable efficiency in producing NPs of metals and metal oxides.[42–44] Algae contain cytotoxic substances, such as laminarians, terpenoids, and fucoidans, which can combat cancer, inhibit proliferation, and suppress tumors.[45–48] Due to their lack of external reducing or capping agents, high energy efficiency, affordability, safety, and simplicity, algae are highly recommended for green NP synthesis in the pharmaceutical and biomedical sectors.[30,48]

The biological synthesis of NPs using microorganisms has gained interest as a sustainable approach for NP production. Bacteria, which can be easily cultured, generate bioactive molecules in liquid form that convert metal ions into metallic NPs.[28,49,50] The cellular mass of bacteria can serve as miniature factories for producing metal oxide NPs.[50–52] These "nano-factories" hold great potential in modern nanotechnology, facilitating the production of various types of NPs. Typically, green NPs are derived from live cells, bioactive molecules isolated from biological systems, or cell-free supernatants.[53] Although the precise production process is not yet fully understood, essential enzymes have been found to contain amino and carboxylic groups that bind to metal ions and subsequently reduce them into metal NPs.[54,55] Biological green approaches use plants, plant extracts, or microorganisms to generate NPs as environmentally friendly alternatives to chemical and physical processes. Utilizing microorganisms in NPs production requires complex procedures for maintaining cell cultures and several purification steps.[56]

Besides being expensive and time-consuming, common methods like chemical precipitation generate dangerous chemical species that stick to surfaces and harm healthcare applications.[56,57] Solvent-based techniques, such as solvothermal,[58] hydrothermal,[59,60] sol-gel,[61,62] chemical precipitation,[63] are among the most frequently employed strategies for producing ZnO NPs. Some reactions require air and heat to initiate, while others need a nonreactive environment and employ lethal compounds like hydrogen sulfide ($H_2S$) and toxic stabilizers. These compounds used to stabilize NPs are poisonous and have harmful consequences.[64] Hazardous substances generated through chemical processes are surface-absorbable and negatively affect medical applications.[64]

To address these issues, eco-friendly NP production technology has been developed. Green NPs utilize harmless, non-hazardous, and eco-friendly compounds.[56] Gelatin is used as a stabilizing agent when the sol-gel method is modified for producing ZnO NPs.[65] These ZnO NPs display a hexagonal (Wurtzite) morphology and range from 30–60 nm in diameter. Studies in the impact of varying oxidation temperatures on the structure of ZnO NPs suggest that gelatin holds significant potential as a stabilizing agent in the sol-gel method for generating ZnO particles at the nanoscale.[63,65] Due to

the high costs and requirements associated with chemical solvents as reducing agents in conventional methods,[66] green methods have been used to synthesize ZnO NPs in a flower-shaped form that has garnered increased attention. ZnO NPs have been exploited in various industrial sectors, including pharmaceuticals, cosmetics, antibacterial products, textiles, and automotive industries.[56,67] Recent studies indicate that ZnO NPs have superior antibacterial capabilities compared to microparticles.[68]

Eco-friendly materials like algae, bacteria, fungi, plant leaf extract, natural materials, and biopolymers, offer several advantages in the production of ZnO NPs by leveraging the inherent qualities of microorganisms and plant, especially for pharmaceutical and medical applications.[56,67] ZnO NPs serve as fillers in medicinal products, cosmetics, and medication carriers.[69] Compared to AgNPs, ZnO NPs are cost-effective and have a desirable white appearance.[70] Plant extract are widely used methods to manufacture ZnO NPs. *Aloe barbadensis* leaf extract was used for fabricating ZnO NPs, yielding spherical and highly stable particles with sizes ranging from 25–40 nm. Adjusting the quantity of leaf broth solution can modulate particle size.[71] Algal-based synthesis is another method, where biological catalysts offer greater specificity and control, allowing customization of NP properties.[72,73] Overall, green synthesis techniques for producing ZnO NPs offer sustainable methods utilizing enzymatic, plant, microbial, and algae systems, highlighting their potential for eco-friendly nanomaterials and encouraging further research for diverse applications in biomedical sciences, sensor technology, catalysis, and other fields.[73]

## Biosynthesis of ZnO NPs Using Bacteria

Biological methods offer a promising alternative for synthesizing NPs, presenting clear benefits over other approaches due to their safety, simplicity, non-toxic nature, eco-friendliness, biocompatibility, and cost-effectiveness.[74] This process utilizes biologically active materials from microorganisms or plant extracts to create ZnO NPs. These materials serve dual roles in NP synthesis, acting as both reducing and capping agents. Typically, the biosynthesis of ZnO NP synthesis involves a metal precursor, such as soluble salts, into prepared biological extracts.[74] The reaction leads to a color change, resulting in ZnO NPs powder.[74]

Microbial fabrication of ZnO NPs can be classified into intracellular and extracellular synthesis. In intracellular synthesis, Zn precursor molecules are taken up by microbial cells, reduced and then extruded as ZnO NPs.[72] For instance, *Lactobacillus paracasei* from dairy products can produce spherical ZnO NPs intracellularly, while *Bacillus licheniformis* and *Bacillus subtilis* can synthesize them extracellularly.[72–79]

The process begins with bacterial isolation and purification on nutrient agar plates using the serial dilution method, followed by incubation at 35–37°C for 24 hours.[73] Pure colonies are then cultured for ZnO NPs production. Each bacterial strain is in nutrient broth (at 35–37°C for 24 hours) under shaking conditions. The supernatant is then used for ZnO NP synthesis, where zinc sulfate ($ZnSO_4$) and sodium hydroxide are mixed with the culture filtrate, followed by heating, microwaving, and cooling to facilitate NP formation.[73] The resulting white deposition is then washed, centrifuged, and oven-dried at 40°C for 8 hours to obtain powdered ZnO NPs. The NPs are stored for further study, and the most potent bacterial strain is identified.[72,75] Table 1 illustrates the various bacterial strains suitable for environmentally friendly ZnO NPs synthesis.

## Biosynthesis of ZnO NPs Using Fungi

Fungal biomass serves as a readily available and renewable resource for producing nanostructured ZnO using an eco-friendly synthesis method.[76] This fungal synthesis technique is similar to microbiological procedures, including the isolation and culture of fungi in typical fungal extract preparations.[76] During cultivation, the fungal strain is maintained in a sterile environment at a controlled temperature. After a set period, the liquid medium, free of cells but rich in fungal byproducts, is separated by filtration and centrifugation. This solution is then used to produce ZnO NPs.[77]

Among various fungi, *Aspergillus niger* is frequently used as the eco-friendly synthesis of ZnO NPs. Successful syntheses have been achieved using *A. niger* and *Aspergillus terreus*, which act as biological reducing and capping agents.[75] Biomass from fungal strains such as *Fusarium oxysporum, Penicillium citrinum, Aspergillus fumigatus, Aspergillus tubulin, and A. niger*, can be cultivated in malt glucose yeast peptone (MGYP) broth. These strains are isolated from soil with high HM contamination, unlike standard strains of *A. tubulin, A. fumigatus, F. oxysporum*, and *P.*

**Table 1** Green Synthesis of ZnO NPs Using Bacteria

| Types of bacteria | Substrate | Conditions | Size | Shape | References |
|---|---|---|---|---|---|
| *Aeromonas hydrophila* | ZnO | Cultivation at 37°C for 1 day | 57.72 nm | Spherical and oval | [80] |
| *Bacillus haynesii* | $ZnSO_4$ | Cultivation at 55°C and centrifugation to obtain filtrate devoid of cells | 45–55 nm | Spherical | [81] |
| *Bacillus licheniformis* | $Zn(CH_3CO_2)_2$ | Cultivation at 36–38°C for 36 hours and centrifugation to obtain bacterial biomass | 300 nm | Flower | [82] |
| *Bacillus megaterium* | $Zn(NO_3)_2$ | Cultivation and centrifugation to obtain filtrate devoid of cells | 45–95 nm | Cubic and rod | [83] |
| *Halomonas elongata* | $ZnCl_2$ | Cultivation at 37°C for 1 week and centrifugation to obtain filtrate devoid of cells | 10–27 nm | Spherical | [84] |
| *Lactobacillus paracasei* | $Zn(NO_3)_2$ | Cultivation at 37°C for 1 day and centrifugation to obtain bacterial biomass | 1180 nm | Spherical | [85] |
| *Lactobacillus plantarum* | $ZnSO_4$ | | 124 nm | – | [86] |
| *Lactobacillus plantarum* | $ZnCl_2$ | Cultivation at 37°C for 1 day and centrifugation to obtain filtrate devoid of cells | 48 nm | Rod | [87] |
| *Pseudomonas aeruginosa* | $Zn(NO_3)_2$ | Cultivation at 33–37°C for 1 day, centrifugation to obtain filtrate devoid of cells and solvation using chloroform | 50–100 nm | Pseudospherical | [88] |
| *Pseudomonas aeruginosa* | $Zn(NO_3)_2$ | Cultivation at 29–31°C for 4 days, centrifugation to obtain filtrate devoid of cells and solvent evaporation using chloroform-ethanol | 35–80 nm | Spherical | [89] |
| *Pseudomonas putida* | $Zn(NO_3)_2$ | Cultivation at 37°C for 1 day and collection of broth culture | 44.5 nm | Spherical | [90] |
| *Rhodococcus erythropolis* | $Zn(CH_3CO_2)_2$, $ZnSO_4$,$Zn(NO_3)_2$, $ZnCl_2$ | Overnight cultivation and collection of broth culture | 50–150 nm | – | [91] |
| *Rhodococcus pyridinivorans* | $ZnSO_4$ | Cultivation at 30°C for 1 day and collection of broth culture | 100–120 nm | Spherical | [92] |
| *Streptomyces Enissocaesilis* | $ZnSO_4$ | Cultivation at 30°C for 3 days and centrifugation to obtain filtrate devoid of cells | 5–20 nm | Spherical | [93] |

(*Continued*)


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**Table 1** (Continued).

| Types of bacteria | Substrate | Conditions | Size | Shape | References |
|---|---|---|---|---|---|
| *Streptomyces* sp. | $ZnCl_2$ | Cultivation at 28°C for 1 week, and centrifugation to obtain filtrate devoid of cells | 20–50 nm | Spherical | [94] |
| *Streptomyces* sp. | $Zn(CH_3CO_2)_2$ | Cultivation at 28°C for 3 days and centrifugation to obtain filtrate devoid of cells | 16–25 nm | Spherical | [76] |
| *Priestia megaterium* | $ZnSO_4$ | Cultivation at 35°C for 2 days and collection of broth culture | 5.77–13.9 nm | Semi-sphere | [95] |
| *Lactobacillus* sp. | $Zn(CH_3CO_2)_2$ | Cultivation at 37°C for 1 days and centrifugation to obtain filtrate devoid of cells | 32 nm | Spherical | [96] |
| *Acetobacter xylinum* | $Zn(CH_3CO_2)_2$ | Cultivation at 50°C for 2 hours and collection of broth culture | 9.8–23.8 nm | Fibers | [97] |
| *Marinobacter* sp. 2C8 | $ZnSO_4$ | Cultivation at 30°C for a day and centrifugation to obtain filtrate devoid of cells | 6–17 nm | Spherical | [98] |
| *Vibrio* sp. VLA | $ZnSO_4$ | | 13–33 nm | Spherical | [99] |

**Abbreviations**: ZnNPs, zinc nanoparticles; ZnO, zinc oxide; $ZnSO_4$, zinc sulfate; $Zn(CH_3CO_2)_2$, zinc acetate; $Zn(CH_3CO_2)_2.2H_2O$, zinc acetate dihydrate; $Zn(CH_3CO_2)_2.6H_2O$, zinc acetate hexaihydrate; $Zn(NO_3)_2$, zinc nitrate; $ZnCl_2$, zinc chloride.

*citrinum*. The fungi are grown in 250 mL Erlenmeyer flasks containing 50 mL liquid medium with glucose (15.0 g), yeast extract (1.0 g), $(NH_4)_2SO_4$ (1.0 g), $MgSO_47H_2O$ (0.1 g), $K_2HPO_4$ (2.0 g), and $KH_2PO_4$ (7.0 g) per liter.[78] Incubation occurred at 28 ± 2°C and 180 rpm for 5 days. The fungal biomass is then washed and transferred to deionized water for further incubation. After this period, the biomass is filtered, and the cell-free filtrate is used for ZnO NP biosynthesis.[78] Each treatment involves mixing 10 mL of 3.0 mM $ZnSO_4$ solution with 10 mL of fungal filtrate, adjusting the pH to 6.5, and incubating in an orbital shaker for 72 h in the dark.[78] The formation of NPs is indicated by a whitish precipitate at the flask's base, which is separated by centrifugation at 10,000 rpm for 10 min. Positive and negative controls are maintained by incubating fungal mycelium with deionized water and $ZnSO_4$ solution, respectively.[78]

This promising, eco-friendly, and cost-effective approach in nanotechnology faces several limitations and challenges. One significant issue is the extended incubation times required for fungal cultures, which generally grow more slowly than bacterial cultures.[79] This necessitates longer periods for NP synthesis and involves extensive trial and error to optimize conditions for maximum yield and desired NP properties.[79] In addition, fungal synthesis requires specific environmental conditions, including precise temperature and pH ranges, as well as a balanced supply of nutrients. Deviations from these conditions can lead to suboptimal synthesis or even complete failure of the process.[79]

Yield variations also pose a challenge, as different fungal strains exhibit varying capabilities for synthesizing ZnO NPs.[100,101] These results leads to inconsistencies in yield and NP properties. Moreover, factors such as medium composition, aeration, and light exposure significantly affect the yield and quality of ZnO NPs, making reproducibility difficult.[102] These biological variabilities complicate the scaling up of the process for industrial applications.[100,102]

Post-synthesis, the purification and processing of NPs to remove biological contaminants is often complex and involves multiple steps. Controlling the size and shape of ZnO NPs is crucial for their applications; However, achieving uniformity remains challenging with biological synthesis methods.[102]

Environmental and health concerns must also be addressed, necessitating strict biosafety measures to prevent contamination and mitigate potential health risks associated with handling live fungal cultures.[101] Although the method is environmentally friendly, the disposal of fungal biomass and by-products must be managed carefully to avoid environmental contamination.[101,102] Addressing these limitations requires ongoing research and development to optimize conditions, improve yields, and ensure the consistency and scalability of fungal synthesis of ZnO NPs.[102] Table 2 summarizes studies on the green production of ZnO NPs utilizing fungi.

## Biosynthesis of ZnO NPs Using Plants

The biological synthesis of NPs offers a viable alternative to conventional chemical or physical fabrication techniques.[24,56,129] Most studies focus on eco-friendly methods for producing metal and oxide NPs, highlighting the efficiency and safety of plant-based synthesis.[130] Factors like pH levels and annealing temperature significantly influence the size and morphology of the ZnO NPs. Similarly, gelatin was used as a stabilizing agent in the sol-gel method to produce hexagonal ZnO NPs, which are calcined at various temperatures.[131] Jiménez-Rosado et al[132] have produced ZnO NPs from pepper extracts high in polyphenols, finding that green synthesis may yield pure smaller NPs than chemical methods.[132]

Further studies demonstrated the synthesis of ZnO using plant extracts like *Solanum rantonnetii* and thyme, with varying calcination temperatures affecting the NPs' characteristics.[133] For instance, thyme-synthesized ZnO NPs may exhibit optimal quality of 450°C.[134] Leaf extracts of Turkish pine (*Pinus Brutia*) were also used, showing that the pH levels can significantly alter the morphology and size of ZnO NPs.[135] MuthuKathija et al[136] have utilized *Pisonia alba* leaf extract to produce ZnO NPs with notable ultraviolet–visible (UV-Vis) spectroscopy at 375 nm.

Additional research explored various plant extracts for ZnO NP synthesis, including *Vitex negundo, Trifolium pratense, Lagenaria siceraria*, and green tea leaves, each demonstrating specific applications from antibacterial properties to supercapacitor potential.[137] Other studies highlight the effectiveness of ZnO NPs in treating urinary tract infections and other medical conditions.[138] Table 3 depicts plant species suited for ecologically friendly ZnO NPs production.

**Table 2** Green Synthesis of ZnO NPs Using Fungi

| Types of fungi | Substrate | Effects | Size, shape | Characterization | References |
|---|---|---|---|---|---|
| *Aspergillus fumigatus* | $ZnSO_4$; Zn $(NO_3)_2$ | – | 1.2–6.8 nm, oblate, spherical, and hexagonal forms aggregate | DLS | [103–105] |
| *Aspergillus terreus* | $ZnSO_4$ | Antifungal | 29 nm (XRD), 54.8–82.6 nm (SEM); spherical | SEM, and XRD | [103,104,106,107] |
| *Candida albicans* | ZnO | – | 20 nm (TEM), 15–25 nm (SEM), 25 nm (XRD), hexagonal wurtzite | XRD, SEM, and TEM | [103,104,108,109] |
| *Phanerochaete chrysosporium* | ZnO | Antibacterial against *Staphylococcus aureus* and *Escherichia coli*, and antifungal against *Aspergillus niger, Geotrichum candidum*, and *Phanerochaete chrysosporium* | 50 nm (TEM), hexagonal wurtzite | FTIR, XRD, SEM, and TEM | [110] |
| *Xylaria arbuscula* | – | Antimicrobial, antioxidant, anti-inflammatory, and antidiabetic | 116 nm (SEM), hexagonal wurtzite | SEM, TEM, and XRD | [111] |
| *Aspergillus aeneus* | $Zn(CH_3CO_2)_2$ | – | 100–140 nm, spherical | UV–Vis spectroscopy, FTIR, XRD, TEM, and EDS | [103,112] |
| *Aspergillus niger* | $Zn(NO_3)_2$ | Antioxidant and anticancer | 30–70 nm, spherical | FTIR, SEM, TEM, DLS, and XRD | [103,113] |
| *Aspergillus niger* | $Zn(NO_3)_2$ | Antibacterial and photocatalytic | 53–69 nm, spherical | FTIR | [103,114] |
| *Aspergillus niger* | Zinc chloride | Antibacterial | 41–75 nm, spherical | UV–Vis spectroscopy, and SEM | [103,115] |
| *Aspergillus niger* | $Zn(CH_3CO_2)_2$ | Antibacterial, antioxidant, and anticancer | 80–130, rod and cluster | FTIR, SEM, TEM, DLS, and XRD | [103,111,116] |
| *Cordyceps militaris* | $Zn(NO_3)_2.6H_2O$ | Photocatalytic | 10.15 nm, flower | FE-TEM, XRD, and FTIR | [103,117] |
| *Fusarium keratoplasticum* | $Zn(CH_3CO_2)_2$ | Antibacterial and anticancer | 10–42 nm, hexagonal | TEM, FTIR, XRD, DLS, and zeta potential analyses | [103,118] |
| *Aspergillus niger* | $Zn(CH_3CO_2)_2$ | Antibacterial and anticancer | 8–38 nm, nano-rod | | [103,118] |
| *Alternaria tenuissima* | $ZnSO_4$ | Antimicrobial, antioxidant, anticancer, and photocatalytic | 15.45 nm, spherical | TEM, and FTIR | [77,103] |
| *Penicillium corylophilum* | Zn $(CH_3CO_2)_2.2H_2O$ | Photocatalytic | 9–51 nm, spherical | FTIR, XRD, TEM, SEM, EDX, and XPS | [103,119] |
| *Periconium* sp. | $Zn(NO_3)_2$ | Antimicrobial and antioxidant | 16–78 nm, quasi-spherical | XRD, FTIR, SEM, and TG/DTA | [76,103] |

| | | | | | |
|---|---|---|---|---|---|
| *Agaricus bisporus* | Zn $(CH_3CO_2)_2.2H_2O$ | Antimicrobial and antioxidant | <40 nm, hexagonal | UV–Vis spectroscopy, SEM, EDX, TEM, XRD, and FTIR | [103,120] |
| *Trichoderma harzianum* and *Trichoderma reesei* | $Zn(NO_3)_2.6H_2O$ | Antibacterial | 60–70 nm, crystal planes | UV-Vis spectroscopy, PXRD, FTIR, SEM, EDX, TEM, and SAED | [103,121] |
| *Xylaria acuta* | $Zn(NO_3)_2.6H_2O$ | Antimicrobial and anticancer | 34–55 nm, hexagonal | UV-Vis spectroscopy, FTIR, PXRD, SEM, EDX, DLS, TEM, and SAED | [103,122] |
| *Acremonium potronii* | Zn $(CH_3CO_2)_2.6H_2O$ | Photocatalytic | 13–15 nm, spherical | UV–Vis spectroscopy, FTIR, XRD, SEM, and TEM | [103,123] |
| *Phanerochaete chrysosporium* | Zn $(CH_3CO_2)_2.2H_2O$ | Antimicrobial | 9–35 nm, hexagonal | UV–Vis spectroscopy, TEM, FTIR, EDX, and XRD | [103,124] |
| *Aspergillus terreus* | $Zn(CH_3CO_2)_2$ | Antimicrobial and antioxidant | 30.45 nm, almost spherical with irregular margins | UV–Vis spectroscopy, FTIR, XRD, DLS, and TEM | [103,125] |
| *Aspergillus niger* | $Zn(CH_3CO_2)_2$ | Antimicrobial and anticancer | 20 nm, hexagonal | XRD, TEM, UV-Vis spectroscopy, and FTIR. | [103,126] |
| *Aspergillus niger* | $Zn(NO_3)_2$ | Antibacterial and wound healing | 82–176 nm, quaternary. | UV–Vis spectroscopy, Zetasizer zeta potential analyses, XRD, FTIR, SEM, and EDX | [103,127] |
| *Aspergillus niger* | Zn $(CH_3CO_2).2H_2O$ | Antibacterial and anticancer | 35 nm, spherical | UV–Vis spectroscopy, PXRD, SEM, and TEM | [128] |

**Abbreviations**: ZnNPs, zinc nanoparticles; ZnO, zinc oxide; $ZnSO_4$, zinc sulfate; $Zn(CH_3CO_2)_2$, zinc acetate; $Zn(CH_3CO_2)_2.2H_2O$, zinc acetate dihydrate; $Zn(CH_3CO_2)_2.6H_2O$, zinc acetate hexaihydrate; $Zn(NO_3)_2$, zinc nitrate; $ZnCl_2$, zinc chloride; DLS, dynamic light scattering; UV-Vis spectroscopy, ultraviolet–visible spectroscopy; XRD, X-ray diffractometer; FTIR, Fourier transform infrared; EDS, energy dispersive spectroscopy; FE-TEM, field emission transmission electron microscopy; XPS, X-ray photoelectron spectroscopy; TG/DTA, thermogravimetric/differential thermal analysis; EDX, energy dispersive X-ray; PXRD, powder X-ray diffraction, SAED, selected area (Electron) diffraction; TEM, transmission electron microscopy; SEM, scanning electron microscopy.


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**Table 3** Green Synthesis of ZnO NPs Using Plants

| Types of plants | Substrate | Conditions | Size | Shape | Characterization | References |
|---|---|---|---|---|---|---|
| *Cayratia pedata* | The nitrate derivative of Zinc: Zn $(NO_3)_2.6H_2O$ | A yellow-colored paste was obtained by reacting 0.1 mM Zn $(NO_3)_2.6H_2O$ with plant extract at various concentrations while keeping the reaction temperature constant at 55, 65, and 75°C. The resultant paste was thoroughly dried, gathered, and prepared for subsequent analysis | 52.24 nm | Horizontal | UV-Vis spectroscopy, FTIR, EDS, XRD, and SEM | [139] |
| *Ficus carica* | Zn $(NO_3)_2.6H_2O$ | A volume of 30 mL of the extract underwent heating at 80°C, with the addition of one gram of $Zn(NO_3)_2.6H_2O$ while stirring continuously. Stirring continued until a yellow paste formed, which was then washed several times with distilled water to eliminate impurities. The resulting $Zn(OH)_2$ NPs were dried at 100°C for 12 hours, followed by calcination at 250°C for 2 hours. This calcination process transformed the product's color to a clear white, indicating the formation of ZnO NPs | 30–40 nm | Tiny spherical clusters | SEM, FTIR, XRD, and EDX | [140] |
| *Acacia caesia* | Zn $(NO_3)_2.6H_2O$ | The NPs were produced at an ideal temperature of 65°C and then subjected to calcination at 400°C | 32.32 nm | Hexagonal | UV-Vis spectroscopy, EDX, FTIR, XRD, and SEM | [141] |
| *Corchorus olitorius* | $Zn(CH_3CO_2)_2$ $.2H_2O$ | A 0.1 M $Zn(CH_3COO)_2 \cdot 2H_2O$ solution was prepared by dissolving it in 50 mL of deionized water. The solution was stirred at room temperature for 30 minutes using a magnetic stirrer until Zn $(CH_3CO_2)_2$ salt fully dissolved. Following this, 20 mL of an aqueous leaf extract was slowly added dropwise to $Zn(CH_3CO_2)_2$ solution while continuing stirring. The mixture was then heated to 60°C and stirred for 4 hours. Subsequently, the heated mixture was further processed on a hot plate until it transformed into a yellowish-brown jelly, indicating the formation of ZnO NPs. The resulting jelly was thoroughly dried and then subjected to calcination at 400°C for 3 hours | 22 nm | Hexagonal wurtzite crystalline | UV–Vis spectroscopy, FTIR, EDX, XRD, and TEM | [142] |
| *Coffea arabica* | Zinc-nitrate hexahydrate | Zn at a concentration of 0.1 M were combined with 20 mL of coffee leaf extract and agitated on a heated magnetic stirrer set to 80°C until a consistent solution was achieved. The mixture was then dehydrated in a hot air oven at temperatures ranging from 120–150° C for 120 minutes. The resulting NPs exhibited a yellow hue and were subsequently crushed in a metallic mortar and pestle to obtain a green preparation of ZnO NPs | ~40 nm | Cubic shaped particles | UV-Vis spectroscopy, XRD, and SEM | [143] |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Annona muricata* (soursop) | Zn $(NO_3)_2.6H_2O$ | Three grams of $Zn(NO_3)_2.6H_2O$ were combined with 50 mL of freshly prepared soursop leaf extract and vigorously stirred for 10 minutes. Then, 20 mL of the mixture were transferred to a sealed tube. The tube was then inserted into the rotor of a commercial microwave oven and subjected to irradiation at 250 watts and 80°C for 15 minutes, resulting in the formation of a reddish-brown solution. After cooling to room temperature, the solution underwent vacuum drying, yielding a dark-brown paste, which was subsequently transferred to a ceramic crucible cup. Finally, the paste underwent calcination in air at 450°C for 2 hours in a temperature-controlled muffle furnace, leading to the production of fine, pale white ZnO powder | 37 nm | Quasi-spherical | FESEM, XRD, TEM, and FTIR | [144] |
| *Cinnamomum camphora* | Zn $(CH_3COO)_2$ | Sixty mL of *C. camphora* leaf extract was mixed with 100 mL of a solution containing 0.25 mol/L $Zn(CH_3COO)_2$. The pH levels were adjusted to 7, 8, and 9 using 1 mol/L NaOH, and the mixture was stirred for 2 hours at temperatures ranging from 60 to 80°C. A similar procedure was carried out at the original pH 6. The formation of ZnO NPs was detected visually through a change in color. Prior experimentation, the ratio of leaf extract to $Zn(CH_3COO)_2$ solution, was optimized. To further refine the synthesis process, additional parameters, including volume ratio (1:5, 2:5, 3:5, and 4:5) of leaf extract to $Zn(CH_3COO)_2$ solution, reaction temperature (40, 60, 80, and 100°C), and reaction time (0.5, 1, 2, and 3 hours) were varied individually while keeping other factors constant. Analysis of UV-Vis spectroscopy indicated that the optimal conditions were a leaf extract/$Zn(CH_3COO)_2$ solution ratio of 3:5 (v/v), a reaction temperature of 60–80°C, and a reaction time of 2 hours. Following synthesis, the reaction mixture underwent centrifugation at 6000 X *g* for 15 minutes, and the resulting precipitate was washed with distilled water and ethanol. Finally, the precipitate was collected and heated at 400°C for 2 hours | 13.92 nm (pH 7), 15.19 nm (pH 8) and 21.13 nm (pH 9). | Spherical | EDX, UV–Vis spectroscopy, SEM, XRD, TEM, and FTIR | [145] |
| *Grewia flavescens* | Zn $(NO_3)_2.6H_2O$ | A 30 mL of plant extract was combined with 3 g of v salt, and the resulting mixture was agitated in a round bottom flask for 4 hours within a temperature range of 70–80°C. After transforming the reaction mixture into a deep yellow paste, the product was dried at 70°C for 6 hours, followed by calcination at 300°C for 3 hours. Consequently, powdered ZnO NPs were obtained. This procedure facilitated the preparation of ZnO NPs utilizing *G. flavescens* leaf extract | 20–30 nm | Spherical | UV–Vis spectroscopy, TGA/DTA, TEM, XRD, DLS, and FTIR | [146] |

(*Continued*)


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**Table 3** (Continued).

| Types of plants | Substrate | Conditions | Size | Shape | Characterization | References |
|---|---|---|---|---|---|---|
| *Carica papaya* | Zn $(CO_3COO)_2$ $.6H_2O$ | A 0.1 M solution of $Zn(CH_3COO)_2.6H_2O$ was prepared by dissolving 2.3 grams of the salt in 10 mL of distilled water within a round-bottomed flask. This flask was then immersed in an oil bath at 60°C. Following this, 40 mL of leaf extract were introduced into the zinc solution, and the resulting mixture was stirred vigorously at 2000 rpm for a duration of 15 minutes. The biomolecules present in the extract served as both capping and reducing agents. Subsequently, the pH of the solution was adjusted to 9 by cautiously adding drops of 0.2 M NaOH. The formed precipitates were collected using centrifugation, cleaned with ethanol and distilled water, and dried. The dried precipitate was crushed and powdered to obtain ZnO. The prepared ZnO was stored in an airtight container for characterization and application. The use of 40 mL of *C. papaya* leaf extract yielded 300 mg ZnO NP, ie, an average of 20.7 mg NPs/mg of leaf extract | ~21 nm | Spherical, semi-spherical, hexagonal, and rod-like | HRTEM, XPS, UV–Vis spectroscopy, FTIR, EDX, TEM, SEM, and XRD | [147] |
| *Solanum rantonnetii* | Zn $(CH_3COO)_2$ $.2H_2O$ | A solution comprising 10 g $Zn(CH_3CO_2)_2.2H_2O$, was prepared by dissolving it in 100 mL of deionized water at 27°C under stirring with a magnetic bar. Subsequently, an aqueous extract obtained from *S. rantonnetii* leaves was cautiously added dropwise to the Zn solution until the solution transitioned from colorless to white and suspended particles formed. The mixture was allowed to stand overnight and then filtered to isolate the suspended particles, which were subsequently dried in an oven at 80°C for 4 hours | 12 nm | Spherical | UV–Vis spectroscopy, TEM, SEM, FTIR, and XRD | [67] |
| *Dysphania ambrosioides* | Zn $(NO_3)_2.6H_2O$ | Ten grams of dried *D. ambrosioides* leaves were soaked in 100 mL of deionized water for one hour at room temperature without agitation. Subsequently, the mixture was agitated for 2 hours at 40°C and 50 rpm. The preparation involved combining 20 mL of the previously obtained extract (pH 6.8) with 1.5 g of $Zn(NO_3)_2.6H_2O$ and stirring for 10 minutes at room temperature (pH 3.6), followed by placement in a muffle furnace for 1 hour at 200, 400, 600, and 800°C. Afterward, the material was removed from the furnace and cooled to room temperature. The resultant powders from each synthesis were washed thrice with deionized water and left to air dry at room temperature for 24 hours | 7–130 nm | Hexagonal prism, and quasi-spherical | TG/DTA, HRTEM, FESEM, FTIR, EDS, TEM, and XRD | [148] |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Punica granatum* | Zn $(CH_3COO)_2$ $.2H_2O$ | Ten mL of aqueous extract from *P. granatum* peel was mixed with 90 mL of distilled water containing the metal precursor Zn $(CH_3CO_2)_2.2H_2O$. The pH of the mixture was adjusted to 8.0 by adding drops of 1N NaOH while stirring at 40°C for one hour. Subsequently, the mixture was left to incubate overnight at room temperature in darkness. The formation of ZnO NPs was indicated by the appearance of a yellowish-white precipitate. The precipitate was separated through centrifugation, washed three times with deionized water, and then dried in an oven at 200°C for three hours | 10–45 nm | Spherical, well arranged, and crystallographic | UV-Vis spectroscopy, EDX, SEM, TEM, XRD, and FTIR | [149] |
| *Daphne oleoides* | Zn $(NO_3)_2.6H_2O$ | A solution of $Zn(NO_3)_2$ was stirred with silica gel. Then, the *D. oleoides* extract was added and stirred continuously until a white precipitate was formed. The precipitate was heated at 200°C for calcination, and ZnO/SG nanocomposite was obtained | 38 nm | Spherical | FTIR, XRD, EDS, FESEM, and BET | [150] |
| *Vitis vinifera* | Zn(II) chloride dehydrate $(ZnCl_2.2H_2O)$ | ZnO NPs were synthesized using a solution containing 0.1 M zinc chloride dihydrate, along with 40 mL of grape extract. Additionally, a 1 M NaOH solution was introduced during mixing to adjust the pH of the mixture to pH 8.0 as required. The resulting mixture was stirred for 2 hours at a constant temperature of 60°C. During this process, the color of the mixture transitioned from yellowish white to white, confirming the formation of ZnO NPs. The resulting solution was isolated by centrifuging at 5000 rpm after cooling to room temperature | 40–60 nm | Hexagonal (wurtzite) crystalline | SEM, FTIR, XRD, AFM, and TEM | [151] |
| *Capparis zeylanica* | $Zn(CH_3CO_2)_2$ $.2H_2O$ | Fifty mL of the leaf extract was mixed with 0.2 M Zn $(CH_3CO_2)_2.2H_2O$, and the solution was dissolved using a magnetic stirrer at 80°C for 2 hours. The formed light-yellow colored precipitate was then allowed to settle for 18 hours. The mixture underwent centrifugation at 10,000 rpm for 25 minutes to isolate the precipitate, which was then repeatedly washed with distilled water to eliminate impurities. Subsequently, it was dried in a hot air oven at 90°C overnight. The calcination process further eliminated crystallinity and organic impurities by subjecting the powder to 400° C for 2 hours | 32–40 nm | Spherical | PL emission, SEM, EDX, XRD, UV–Vis spectroscopy, FTIR, AFM, and TEM | [152] |

(*Continued*)



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**Table 3** (Continued).

| Types of plants | Substrate | Conditions | Size | Shape | Characterization | References |
|---|---|---|---|---|---|---|
| *Tecoma castanifolia* | $ZnSO_4$ | To synthesize ZnO NPs, a combination of 10 mL of plant extract was thoroughly blended with 90 mL of $ZnSO_4$ solution. This amalgam was left to incubate at room temperature for a duration of 4 days while being periodically examined for NP formation visually and via UV–Vis spectroscopy. Following the 4-day incubation period, the mixture underwent centrifugation at 5000 rpm for 15 minutes. The resulting pellet was gathered and reconstituted in distilled water for subsequent centrifugation. The collected pellet was processed repeatedly twice or thrice to remove the impurities present in it. Finally, the obtained pellet was dried in hot air oven till the moisture is completely removed | 70–75 nm | Spherical | FTIR, XRD, EDX, TEM, and UV–Vis spectroscopy | [153] |
| *Cratoxylum formosum* | $Zn(CH_3CO_2)_2$ | At room temperature, continuous stirring was maintained while gradually combining 100 mL of *C. formosum* extract at concentrations of either 2 or 6 mg/mL with an equal volume of 0.2 M $Zn(CH_3CO_2)_2$ solution. Next, 0.2 M of NaOH was added dropwise into the mixture until it reached pH 12. The mixture was stirred for 1 hour, then precipitates were collected after centrifugation at 8000 rpm, 4°C for 30 minutes. Next, the precipitates were incubated at 80°C overnight. Subsequently, a dry powder was obtained and designated as TGS-Cf2 and TGS-Cf6 according to green synthesis with concentration of *C. formosum* crude extract at 2 and 6 mg/mL, respectively | 150–900 nm | Spherical or sheet-like structures (depending on synthesis process and concentration of crude extract) | FTIR, SEM, and UV–Vis spectroscopy | [154] |
| *Cardiospermum halicacabum* | $Zn(CH_3CO_2)_2$ | ZnO NPs were synthesized following the method outlined by Duan et al[155] | 10–20 nm | Spherical | UV-Spectroscopy, XRD, TEM, EDX, and FTIR | [155,156] |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Deverra tortuosa* | Zn $(NO_3)_2.6H_2O$ | The crude plant extract (approximately 25 mL) underwent heating (60–80°C) on a magnetic stirrer. Upon reaching a temperature of 60° C, 2.5 grams of $Zn(NO_3)_2.6H_2O$ were introduced and allowed to react for around 1 hour until a white precipitate formed. Subsequently, the mixture was left overnight in a hot air oven at 60°C or until it yielded a creamy paste. This resulting paste was then gathered and subjected to multiple washes using a solution comprised of distilled water and ethanol (in a ratio of 3:1). Following this, the collected paste was transferred into a ceramic crucible cup and subjected to heating in a furnace at 400°C for a duration of 2 hours | 9.26–31.18 nm | Hexagonal | TEM, XRD, FTIR, and UV-Vis spectroscopy. | [156] |

**Abbreviations**: ZnNPs, zinc nanoparticles; ZnO, zinc oxide; $ZnSO_4$, zinc sulfate; $Zn(CH_3CO_2)_2$, zinc acetate; $Zn(CH_3CO_2)_2.2H_2O$, zinc acetate dihydrate; $Zn(CH_3CO_2)_2.6H_2O$, zinc acetate hexaihydrate; $Zn(NO_3)_2$, zinc nitrate; $ZnCl_2$, zinc chloride; DLS, dynamic light scattering; UV-Vis spectroscopy, ultraviolet–visible spectroscopy; XRD, X-ray diffractometer; FTIR, Fourier transform infrared; EDS, energy dispersive spectroscopy; FESEM/FETEM, field emission scanning/transmission electron microscopy; XPS, X-ray photoelectron spectroscopy; TG/DTA, thermogravimetric/differential thermal analysis; EDX, energy dispersive X-ray; HRTEM, high-resolution electron microscopy; BET, Brunauer-Emmett-Teller; PL, photoluminescence; AFM, atomic force microscope; TEM, transmission electron microscopy; SEM, scanning electron microscopy.


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## Biosynthesis of ZnO NPs Using Algae

The eco-friendly production of ZnO NPs through algae represents a sustainable method with potential applications across diverse sectors.[157,158] Algae, abundant and cost-effective biological resources, present a distinct advantage for synthesizing ZnO NPs due to their inherent capacity to generate bioactive substances.[158] This procedure utilizes the bioactive elements in algae, such as pigments and proteins, to reduce Zn precursors and stabilize the resulting NPs. This green method eliminates the need for hazardous chemicals and energy-intensive processes, thus reducing environmental impact.[158]

In addition, the ZnO NPs produced demonstrate improved compatibility with biological systems, showing promise for various applications in medical settings, agriculture, and environmental remediation.[159] The creation of ZnO NPs through green synthesis using algae showcases the seamless fusion of biotechnology and nanotechnology, presenting an innovative and environmentally friendly approach to develop novel nanomaterials.[158,159] Table 4 illustrates the types of algae that can be utilized in the successful green synthesis of ZnO NPs.

# Traditional versus Green Methods in Producing ZnO NPs

Both traditional and green methods have their advantages and challenges in the production of ZnO NPs. Traditional methods offer high yield, consistency, and scalability, but they come with a higher environmental cost.[172] In contrast, green methods, while environmentally friendly and sustainable, face challenges related to scalability and consistency. Addressing these challenges through standardization, optimization, and technological integration can enhance the industrial applicability of green methods, making them a viable alternative to traditional approaches.[172]

Traditional methods, such as chemical precipitation, the sol-gel method, and hydrothermal synthesis, are well-established and widely used in industry.[173,174] These methods are highly effective, providing controlled size distribution and high purity of ZnO NPs. For instance, chemical precipitation involves reacting zinc salts with alkaline agents to precipitate ZnO NPs, resulting in fast reaction rates and high output.[175] Similarly, the sol-gel method produces uniform and pure ZnO NPs through hydrolysis and condensation of Zn precursors.[173] Hydrothermal synthesis, which crystallizes ZnO NPs under high pressure and temperature, allows for excellent control over particle size and morphology.[176] However, these traditional methods often require significant energy consumption to maintain precise temperature and pH conditions, contributing to a substantial carbon footprint.[172,175]

The environmental impact of traditional methods is further compounded by the production of hazardous chemical by-products, necessitating careful waste management.[172] Despite these drawbacks, traditional methods are highly scalable, with established protocols and infrastructure that ensure consistent and reproducible properties of ZnO NPs across batches.[177] However, the costs associated with energy consumption and waste management remain high.

On the other hand, green methods for producing ZnO NPs emphasize sustainability and environmental friendliness. Prominent green methods include microbial synthesis and the use of waste materials.[177] Microbial synthesis employs bacteria, fungi, or algae, harnessing their metabolic activity to biosynthesize ZnO NPs with specific shapes and sizes.[177,178] In addition, utilizing waste materials such as agricultural or industrial by-products can yield functional ZnO NPs, promoting sustainable resource use. These green methods generally require lower energy consumption, resulting in a reduced carbon footprint.[178] They also minimize hazardous chemical waste by utilizing renewable and biodegradable materials, enhancing their sustainability.[178]

Despite their environmental benefits, green methods face significant challenges in industrial applicability.[179] Maintaining consistency and reproducibility at larger scales is difficult due to the inherent variability in biological materials and processes. To overcome this, standardizing biological materials and developing robust protocols are essential.[179] Furthermore, green methods often yield lower outputs compared to traditional methods.[180] Optimizing biological conditions and scaling up cultivation processes can help address this issue. Process control in biological systems is another challenge, which can be mitigated by integrating advanced monitoring and control systems.[179] Although the initial costs for research and development of green methods can be high, investing in pilot projects and forming public-private partnerships can share the costs and risks, making green methods economically viable.[179,180]

# Applications of ZnO NPs in Biomedicine

ZnO NPs, a newer of cost-effective and less hazardous nanomaterial have garnered significant interest in various biomedical fields, including anticancer, antioxidant, anti-inflammatory, antibacterial, and anti-diabetes applications, as well as bioimaging

**Table 4** Green Synthesis of ZnO NPs Using Algae

| Types of algae | Substrate | Effects | Size, shape | Characterization | References |
|---|---|---|---|---|---|
| *Chlamydomonas reinhardtii* | | Photocatalytic | 55–80 nm, nanorod | PXRD, and FTIR | [160] |
| *Sargassum muticum* | $ZnSO_4$ | | 30–57 nm, hexagonal wurtzite | XRD, FESEM, and FTIR | [104,161] |
| *Sargassum myriocystum* | | | 46.6 nm (DLS), 20–36 nm (AFM), spherical | DLS, and AFM | [104] |
| *Gracilaria gracilis* | $Zn(NO_3)_2$ | Photocatalytic | 18 to 50 nm, hexagonal | XPS, TEM, SEM, and XRD | [162] |
| *Caulerpa peltata, Sargassum myriocystum* | $Zn(NO_3)_2$ | Antibacterial | 36 nm, spherical, radial, triangle, rod, rectangle | EDX, FTIR, XRD, TEM, SEM, AFM, and DLS | [163] |
| *Sargassum wightii* | $Zn(NO_3)_2$ | Antimicrobial | 20–62 nm, spherical | FTIR, EDX, SEM, XRD, and UV–Vis spectroscopy | [164] |
| *Ulva lactuca* | $Zn(CH_3CO_2)_2$ | Photocatalytic, antibiofilm, and larvicidal | 10–50 nm, sponge-like asymmetrical shaped | SAED, TEM, FTIR, UV–Vis spectroscopy, and PXRD | [69] |
| *Ulva fasciata* | $Zn(CH_3CO_2)_2$ | Antibacterial | 77.81 nm, spherical | FTIR, XRD, EDX, SEM, zeta potential, and particle size distribution | [165] |
| *Gracilaria edulis* | | Anticancer, and antioxidant | 65–95 nm, rod-shaped | FESEM, EDX, FTIR, and XRD | [166] |
| *Agathosma betulina* | Hydrated Zn $(NO_3)_2$ | – | 15.8 nm | RS, attenuated total reflection IR, XRD, EDX, and TEM | [167] |
| *Gracilaria edulis* | $ZnSO_4$ | Antimicrobial | 66–95 nm, rod shaped | XPS, TEM, FTIR, FESEM, and XRD | [168] |
| *Chlorella* sp. | | Antioxidant | 20–50 nm | UV-Vis spectroscopy, FTIR, XRD, EDX, and TEM | [169] |
| *Sargassum muticum* | Zn $(NO_3)_2.6H_2O$ | Antimicrobial, antibacterial, and photocatalytic | 15–50 nm, spherical | FTIR, RS, XRD, and DLS | [170] |
| *Oedogonium* sp. | $Zn(CH_3CO_2)_2$ | Antimicrobial | 2–20 nm, spherical | UV–Vis spectroscopy, FT-IR, and SEM | [171] |

**Abbreviations**: ZnNPs, zinc nanoparticles; ZnO, zinc oxide; $ZnSO_4$, zinc sulfate; $Zn(CH_3CO_2)_2$, zinc acetate; $Zn(CH_3CO_2)_2.2H_2O$, zinc acetate dihydrate; $Zn(CH_3CO_2)_2.6H_2O$, zinc acetate hexaihydrate; $Zn(NO_3)_2$, zinc nitrate; $ZnCl_2$, zinc chloride; DLS, Dynamic Light Scattering; UV-Vis spectroscopy, ultraviolet–visible spectroscopy; XRD, X-ray diffractometer; FTIR, Fourier transform infrared; FESEM/FETEM, field emission scanning/transmission electron microscopy; XPS, X-ray photoelectron spectroscopy; EDX, energy dispersive X-ray; PXRD, powder X-ray diffraction, SAED, selected area (Electron) diffraction. AFM, atomic force microscope; RS, Raman spectroscopy; TEM, transmission electron microscopy; SEM, scanning electron microscopy.


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and drug delivery.[181] This section highlights current developments in the biological uses of ZnO NPs. Nanotechnology in medical research has facilitated a deeper understanding of molecular biology, potentially enabling the design of novel therapies for diseases that were previously difficult to target due to size limitations.[182] The creation of bio-functional NPs is crucial for biomedical purposes, attracting significant interest from numerous research teams in recent years.[183]

Various materials and chemical manufacturing techniques for biomedical applications of ZnO NPs are currently under investigation.[182,183] Zn, a natural element found in all living organisms, is essential for the metabolic processes of humans, animals, and plants.[2] All living organisms require exposure to the biosphere's normal background levels of Zn. ZnO is extensively used in the medical, pharmaceutical, and cosmetic sectors and is recognized for its beneficial use as a dietary supplement.[183] Although inhaling ZnO dust and fumes is generally considered harmless, precautions must be taken to avoid it. Consequently, regulations have been established to limit potential exposure.[184] The biological activities of various green ZnO nanoparticles are outlined in Table 5.

**Table 5** Biological Activities of Different Green ZnO NPs

| **Anticancer activity** | | | |
|---|---|---|---|
| **Green ZnO NPs** | **Cancer cell lines** | **Mechanism** | **References** |
| *Punica granatum* peels extract | Colorectal, lung, and cervical cancers | Potentiate cell death through ROS-mediated apoptotic process | [185] |
| *Pruinosum* extract | Skin cancer, lung fibroblast | Generating ROS in cancer cells will induce apoptosis in cancer cells | [186] |
| *Sargassum muticum* | Liver cancer | Reducing angiogenesis and promoting apoptosis | [187] |
| Pumpkin seed extract | Breast cancer | Inducing apoptosis, generating high levels of ROS, leading to cell death | [188] |
| *Echinacea purpurea* extract | Breast cancer | Showing antioxidant activity | [189] |
| Zn ferrite NP sing *Lawsonia inermis* leaves | Breast cancer cells | Lowering the viability of cancer cells by prompting apoptosis is achieved by producing ROS inside the cells. Increased ROS levels result in oxidative stress, causing harm to cellular structures and initiating pathways leading to apoptosis | [190] |
| *Rehmanniae radix* | Bone cancer cells | Enhancing the generation of ROS while decreasing mitochondrial membrane potential levels. Elevating the expression of apoptotic proteins like Bax, caspase-3 and −9 to facilitate apoptosis | [191] |
| Seed extract of *Lepidium sativum* | Colorectal cancer | Downregulating Bcl 2 gene and upregulating p53 gene expression. Promoting apoptosis through cell cycle arrest, DNA degradation. Inducing apoptosis transcription factor such as Bax gene | [192] |
| Stem bark extract from *Amygdalus scoparia* | Vero cell lines, MCF-7, Hela, and LS180 | When ZnO NPs are absorbed into lysosomes. The acidic pH of the lysosomes can liberate the harmful ions, resulting in increasing cellular ROS. Decreasing cancer cell viability. Inducing apoptosis | [193] |
| *Raphanus sativus var. longipinnatus* | Lung cancer | Promoting cell cycle arrest. Inducing apoptosis | [193] |
| Aerial parts of *Deverra tortuosa* | Adenocarcinoma | Generating ROS, and promoting phagocytosis | [194] |
| Leaves of *Laurus nobilis* | Lung cancer cells | Generating intracellular ROS. Dysfunction of the mitochondria and promoting cell death | [195] |
| Leaves of *Eclipta prostrata* | Human liver carcinoma | The zinc ions released intercellularly will be followed by releasing the ROS with more amounts than the normal cells, promoting to more oxidative stress in cancer cells compared to the normal cells | [196] |

(*Continued*)

**Table 5** (Continued).

| Antimicrobial activity | | | |
|---|---|---|---|
| **Green ZnO NPs** | **Microorganisms** | **Mechanism** | **References** |
| *Cymbopogon citratus* extract | *Escherichia coli* and *Staphylococcus aureus* | Showing bactericidal activity on both Gram-negative and Gram-positive bacteria. The activity was determined through the disc diffusion method | [197] |
| | | Producing ROS when in contact with bacteria. ROS, such as hydrogen peroxide and superoxide radicals, promote oxidative stress in bacterial cells, damaging cellular components like DNA, lipids, and proteins | |
| Plantain peel extracts | *Salmonella enterica, Klebsiella pneumoniae Staphylococcus aureus*, and *Bacillus cereus* | Causing cell membrane disruption: interacting with bacterial cell membranes. This interaction may result in structural damage to the membrane, compromising its integrity. This disruption can increase the permeability, leak cellular contents, and ultimately induce bacterial cell death. Causing inhibition of enzyme activity may interfere with key enzyme activity within bacterial cells. By disrupting enzymatic processes vital for the survival of bacteria, these NPs can impede essential cellular functions and contribute to antibacterial effects. Causing protein interaction, which may interact with bacterial proteins and affect their structure and function. This interference with protein function can disrupt various cellular processes and contribute to antibacterial activity. Causing metal ion release: Zn ions released from the NPs could potentially contribute to their antibacterial effectiveness. The release of zinc ions can disrupt bacterial homeostasis and interfere with essential cellular functions, contributing to the inhibition of bacterial growth | [198] |
| Propolis extract | *Staphylococcus aureus* | Disrupting bacterial cell membrane. The antibacterial activity is against Gram-negative and Gram-positive | [199] |
| *Elaeagnus angustifolia* leaf extracts | *Klebsiella pneumoniae, Bacillus subtilis, Staphylococcus aureus*, and *Escherichia coli* | Inhibiting both Gram-positive and Gram-negative bacterial growth. Enter the cellular membrane through the present tiny pores in the bacterial cell membrane, misbalancing the minerals and proteins will be leaked leading to bacterial growth inhibition and cell death | [200] |
| *Dysphania ambrosioides* extract | *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Streptococcus mutans, Streptococcus sanguinis, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus epidermidis, Staphylococcus aureus* | Inhibiting both Gram-positive and Gram-negative bacteria. Specific proteins were detected in both Gram-positive and Gram-negative bacteria, such as TagF in *Staphylococcus epidermidis* and AcrAB-TolC in *Escherichia coli*, making them potential candidates for NP targeting | [148] |
| Leaves of *Cassia fistula* | *Escherichia coli* | ZnO NPs exert the antibacterial mechanism by creating ROS such as hydroxyl radicals, hydrogen peroxide, and superoxide anions. Induction of $Zn^{2+}$ ions release. The released $Zn^{2+}$ will interact with bacterial cells, specifically the nucleic acid, cytoplasm and cell membrane. This will disrupt the integrity of cells, leading to cellular death | [201] |

(*Continued*)

**Table 5** (Continued).

| | | | |
|---|---|---|---|
| Leaves of *Pongamia pinnata* | *Escherichia coli* and *Staphylococcus aureus* | Exhibiting potent antibacterial and antifungal properties against a wide range of bacteria and fungi, including *Bacillus subtilis, Salmonella enterica* serovar Typhimurium, *Staphylococcus aureus, Streptococcus pyogenes, Mycobacterium tuberculosis, Escherichia coli, Klebsiella pneumonia, Mycobacterium luteus, Vibrio cholera, Pseudomonas aeruginosa, Salmonella* Paratyphi, *Fusarium oxysporum, Fusarium culmorum, Aspergillus fumigatus*, and *Aspergillus niger*. Showing cell membrane disruption and interaction with bacteria cell membranes. This interaction may result in structural damage to the membrane, compromising its integrity. This disruption can increase the permeability, leak cellular contents, and ultimately induce bacterial cell death. Generation of ROS, such as hydroxyl radicals, hydrogen peroxide, and superoxide anions. Induction of $Zn^{2+}$ ions release. The released $Zn^{2+}$ will interact with bacterial cells, specifically the nucleic acid, cytoplasm, and cell membrane. Causing DNA binding and damage: this may interact with bacterial DNA. This interaction can lead to structural damage to the DNA molecule, interfering with replication and transcription processes. DNA damage is a critical factor in inhibiting bacterial growth and survival | [201] |
| Leaves of *Phyllanthus niruri* | *Staphylococcus saprophyticus* | | [202] |
| Leaves of *Solanum nigrum* | *Pseudomonas aeruginosa* | | [203] |
| Leaves of *Vitex trifolia* | *Escherichia coli*, Salmonella Paratyphi and *Staphylococcus aureus* | | [204] |
| Leaves of *Catharanthus roseus* | *Streptococcus pyogenes*, and *Staphylococcus aureus* | | [205] |
| Flower extract of *Trifolium pratense* | *Escherichia coli, Pseudomonas aeruginosa*, and *Staphylococcus aureus* | | [206] |
| Leaves of *Limonia acidissima* | *Mycobacterium tuberculosis* | | [207] |
| Leaves of *Ceropegia candelabrum* | *Salmonella enterica serotype* Typhi, *Escherichia coli, Bacillus subtilis*, and *Staphylococcus aureus* | | [208] |
| Leaves of *Celosia argentea* | *Acetobacter, Salmonella*, and *Escherichia coli* | | [209] |
| Leaves of *Couroupita guianensis* | *Vibrio cholera, Mycobacterium luteus, Escherichia coli, Klebsiella pneumonia*, and *Bacillus cereus* | | [210] |
| Leaves of *Parthenium hysterophorus* | *Fusarium oxysporum, Fusarium culmorum, Aspergillus fumigatus, Aspergillus niger*, and *Aspergillus flavus* | | [211] |
| Leaves of green tea | *Escherichia coli*, and *Staphylococcus aureus* | | [212] |
| **Anti-inflammatory activity** | | | |
| **Green ZnO NPs** | **Inflammation** | **Mechanism** | **References** |
| Stevia leaf | Various diseases like atherosclerosis, rheumatoid arthritis, asthma, and cancer | Inhibiting the expression of iNOS enzyme. Inhibiting the pro-inflammatory cytokines release. Inhibiting myeloperoxidase. Inhibiting NF-κβ pathway. Inhibiting Mast cell degranulation | [213] |
| *Andrographis paniculata* leaves | Protein denaturation | Inhibiting NO free radical activity. Inhibiting the pro-inflammatory cytokines release | [214] |
| *Polygala tenuifolia* root | Oxidative damage | Reducing the levels of expression of IL-1B gene in a dose-dependent manner. Inhibiting NO production. Inhibiting mRNA expression of the pro-inflammatory cytokines | [215] |
| *Hyssopus officinalis* | Edema | Enhancing levels of the anti-inflammatory cytokine IL-10. Reducing levels of edema | [216] |

(*Continued*)

**Table 5** (Continued).

| | | | |
|---|---|---|---|
| *Kalanchoe pinnata* | Various diseases like atherosclerosis, rheumatoid arthritis, asthma, and cancer | Releasing pro-inflammatory mediators such as TNFα, IL-1β, IL-6. Inhibiting inflammatory cytokines release | [217] |
| *Pelargonium odoratissimum* aqueous leaf extract | Lipid peroxidation and protein denaturation | Inhibiting the pro-inflammatory cytokines release. Inhibiting NF-κβ pathway | [218] |
| *Tabernaemontana heyneana* wall | Oxidative damage | Suppressing the release of neutrophils, bactericidal and fungicidal enzymes. Inhibiting the pro-inflammatory cytokines expression and enzymes involved in inflammation | [219] |
| Bark and leaves of *Heritiera fomes, Sonneratiaapetala* | Protein denaturation | Inhibiting the proinflammatory cytokines release. Suppressing the expression of iNOS enzyme, inhibiting myeloperoxidase, and blocking the NF-jb pathway along with degranulation of mast cells | [220] |

**Abbreviations**: ZnO NPs, zinc oxide nanoparticles; iNOS, inducible nitric oxide synthase; NO, nitric oxide; ROS, reactive oxygen species.

## Anticancer Activity of ZnO NPs

Cancer treatment has traditionally involved surgery, radiation, and chemotherapy.[221–223] However, these treatments often come with severe side effects.[224] ZnO NPs have shown promise due to their selective cytotoxicity towards malignant cells in vitro. Their surfaces can be modified to enhance this selective cytotoxicity, leading to the elimination of cancerous cells without harming healthy cells.[225] Siddiqi et al[226] have reported that ZnO NPs are toxic to both Gram-positive and Gram-negative bacteria and can affect primary human T-cells. ZnO NPs also considered safe to living organisms due to the essential nature of Zn(II) ions for adults. These advantages have spurred research into ZnO NPs for cancer treatment, highlighting their potential as biodegradable and biocompatible nanoplatforms.[224]

ZnO NPs combat tumors by increasing ROS generation and promoting apoptosis.[227] Their electrostatic properties are also beneficial for anticancer effects. Neutral hydroxyl groups attached to ZnO NPs change their surface charge behavior. In a high-pH solution, protons move away from the particle surface, giving the surface oxygen atoms a negative charge. At lower pH values, positively charged zinc hydroxide ($ZnOH_2^+$) forms on the particle surface. ZnO NPs have a positive surface charge and an isoelectric point of 6.4–6.75 in healthy conditions.[228] Cancer cell membranes, however, have a markedly negative potential and contain many anionic phospholipids, such as phosphatidylserine.[229]

The positive charge ZnO NPs enhances their interactions with cancer cells, increasing cellular absorption, cytotoxicity, and phagocytosis.[230] Studies have shown that NPs are harmless to mature human dermal fibroblasts and arterial endothelial cells but are damaging to metastatic tumor cells, and they increase apoptosis in neural stem cells.[231] Nanomedicine based on ZnO NPs offers high biocompatibility, cancer targeting ability, ease of surface functionalization, and drug delivery capability, addressing many of the drawbacks of traditional treatments.[225] However, challenges remain, such as the need for biocompatible dispersion techniques and a better understanding of the specific cytotoxic mechanisms.[225]

Autophagy, a process of cellular self-consumption, can be triggered by stimuli like ROS, dysfunctional organelles, protein aggregation, and certain anticancer drugs. This process can lead to apoptosis in cancer cells by promoting self-degradation.[232] Therefore, autophagy plays a crucial role in NP-induced cytotoxicity by enhancing cancer cell viability and activating death pathways.[232]

Hussein and Mohammed[151] have synthesized ZnO NPs using grape (*Vitis vinifera*) extract and demonstrated their significant inhibitory effect against the bacteria *Staphylococcus aureus* and *Klebsiella pneumoniae*. These ZnO NPs have also shown notable cytotoxic effects against MCF-7 and AMGM5 human cancer cell lines,[151] highlighting their potential in treating both bacterial infections and cancer. Chandrasekaran et al[233] have synthesized ZnO NPs chemically and using plant leaves, and evaluated their anticancer, antidiabetic, and antibacterial properties. The plant-derived green-synthesized ZnO NPs exhibit the highest α-amylase inhibition efficiency and significant cytotoxicity against the MCF7 cell

line.[233] In terms of antibacterial activity, green-synthesized ZnO NPs showed stronger effects against *Salmonella typhi* and *B. subtilis* than to chemically synthesized.[233] This underscores the enhanced antimicrobial efficacy of green-synthesized ZnO NPs, making them promising for further applications in cancer treatment and beyond.[233] The anticancer mechanisms of ZnO NPs are illustrated in Figure 1.

## Delivery of Cancer Drugs Using ZnO NPs

Incorporating ZnO NPs into therapeutic formulations significantly enhances the potential for safer and more efficient cancer therapies. By utilizing NP-based drug delivery to target specific sections of cancer cells, it is feasible to reduce the total quantity of drugs used and minimize unwanted side effects.[234] ZnO NPs are preferable to other nanomaterials because they are less toxic and more biodegradable. There is considerable interest in using ZnO NPs for cancer treatments.[181] Loading drugs such as doxorubicin (DOX), paclitaxel, curcumin, and baicalin onto ZnO NPs can improve their solubility, toxicity, and distribution within cancer cells.[235] Previous studies have suggested that both ROS and autophagy influence ZnO NPs' cytotoxicity, although the specific mechanisms regulating ROS and autophagy remain unidentified.[236]

Using ZnO NPs, researchers have explored the mechanisms governing autophagy and the correlation between ROS and autophagy in lung epithelial cells.[236] Batool and colleagues have synthesized ZnO NPs using *A. barbadensis* leaf extract for stabilization and capping purposes.[237] They determine the drug loading capacity (LC) and loading efficiency (LE) of un-stabilized and polyethylene glycol (PEG)-ZnO NPs with DOX and gemcitabine (GEM). DOX exhibits better LE at 65% (650 mg/g) and LC 32% (320 mg/g) on ZnO NPs than GEM, which showed LE 30.5% (30 mg/g) and LC 16.25% (162 mg/g).[237] Similar findings have been observed for PEG-ZnO NPs, with DOX showing 68 and 35%

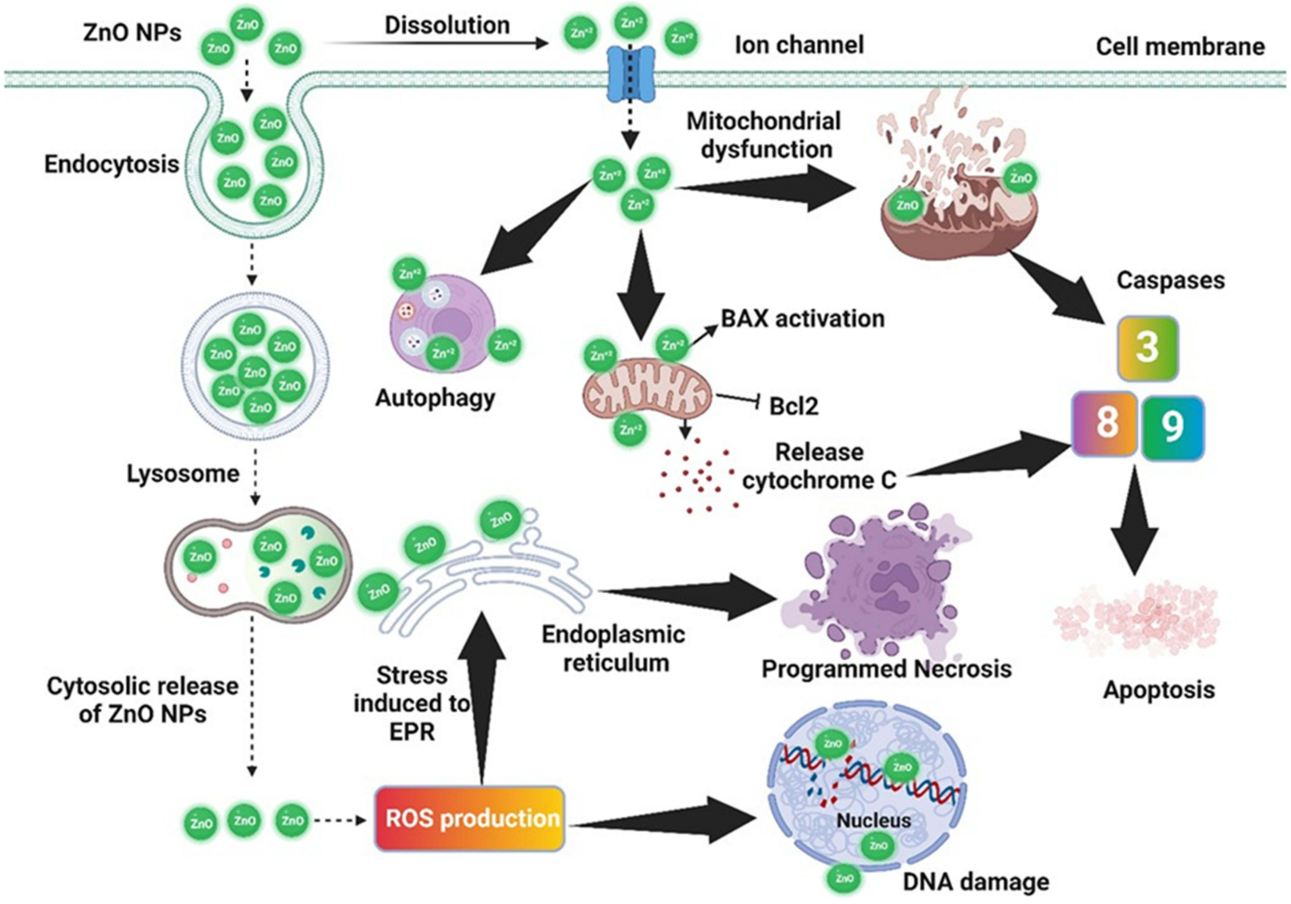


**Figure 1** The anticancer mechanisms of ZnO NPs.
**Abbreviations**: ZnO NPs, zinc oxide nanoparticles; EPR, endoplasmic reticulum.

increases in LE (680 mg/g) and LC (350 mg/g), respectively, compared to GEM, whose LE and LC values increased by 35 (350 mg/g) and 19% (190 mg/g), respectively. Using the 3-(4,5-dimethylthiazol-2-Yl)-2,5-diphenyltetrazolium bromide (MTT) assay, DOX was chosen to encapsulate NPs to assess their in vitro antiproliferative capability against the triple-negative breast cancer (TNBC) cell line (MDA-MB-231).[237]

Gomathi et al[238] have infused DOX into ZnO NPs using the sol-gel process. Various pH conditions (3.0, 6.0, 8.2, and 10.0) have been used to load the drug with a pH of 6.0 determined to be optimal based on UV and SEM analyses. The in vitro cytotoxicity of DOX, ZnO, and ZnO-DOX against HeLa cells is evaluated using the MTT colorimetric cell viability test. ZnO-DOX cells are suppressed by 99.4% at a concentration of 100 g/mL. These findings provide compelling evidence that green biosynthesized ZnO may function well as a potential nano-drug carrier for the targeted drug delivery system.[238] Figure 2 depicts anticancer drug delivery using ZnO NPs in cancer treatment.

## ZnO NPs Cytotoxic Effect on Cancer Cells

ZnO NPs induce the death of cancer cells without harming healthy cells.[239] However, before ZnO NPs can be used in medicine, several challenges must be addressed, such as developing biocompatible dispersion methods and understanding the mechanisms behind their selective cytotoxicity.[181] Research on the cytotoxic effects of ZnO NPs on mammalian cells is limited, and experts do not agree on the significance of existing findings.[181]

Studies have shown that ZnO NPs reduce the viability of primary human T cells at concentrations lethal to both Gram-negative and Gram-positive bacteria.[240] Despite numerous reports indicating that these NPs do not harm cultured human dermal fibroblasts, they are toxic to cancerous and vascular endothelial cells and induce apoptosis in brain stem

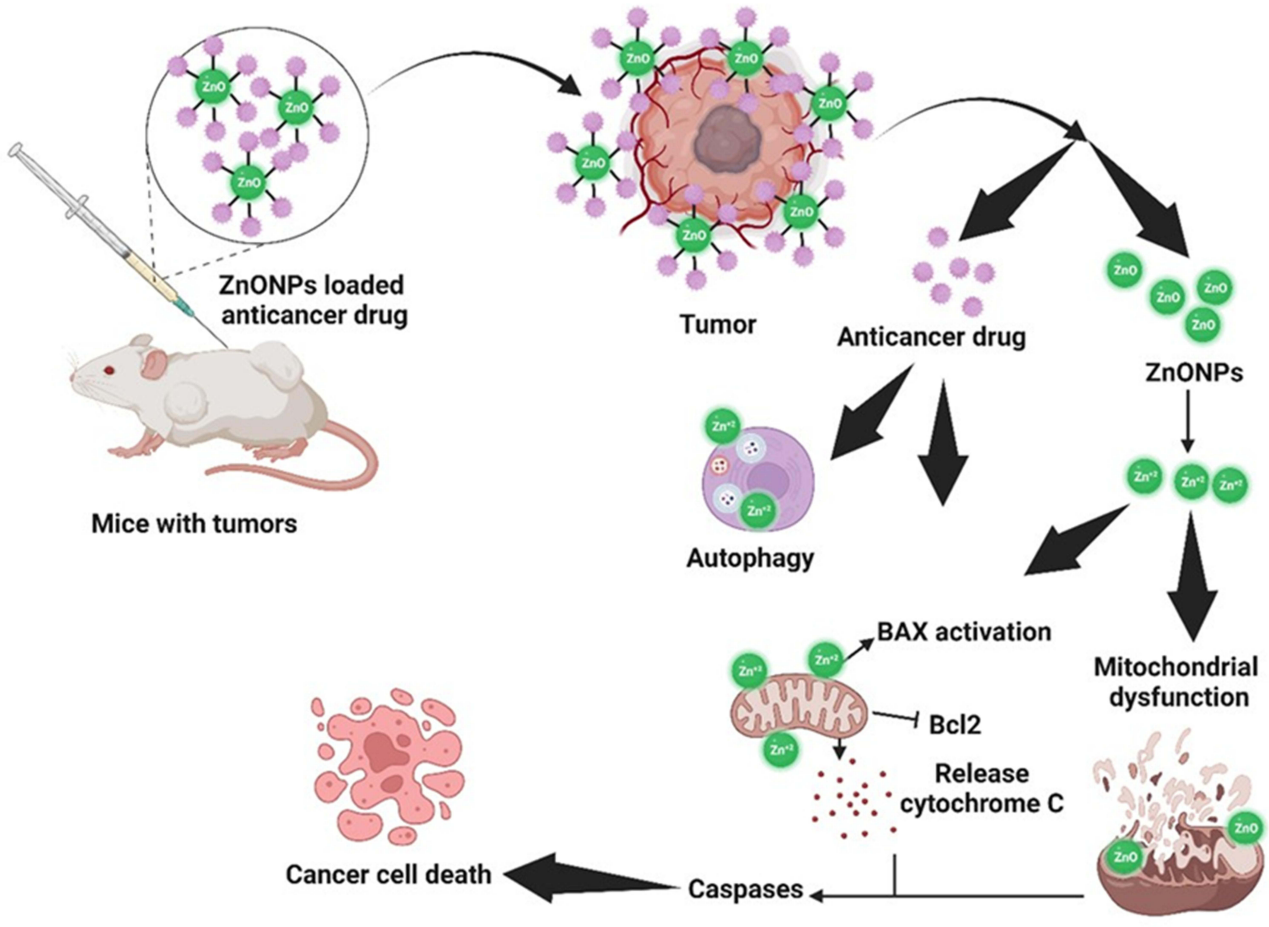


**Figure 2** Anticancer drug delivery of ZnO NPs in cancer treatment.
**Abbreviation**: ZnO NPs, zinc oxide nanoparticles.

cells.[137] The size of NPs also influences their impacts on cell survival. Van Giau et al[138] found that ZnO NPs measuring 8 nm were more toxic to *S. aureus* than between 50–70 nm. Youssef et al[232] observed an inverse relationship between NP size and toxicity in certain cells, specifically noting that smaller NPs generate more ROS.[232] Sudhakaran et al[241] demonstrated that ZnO NPs are toxic to neural stem cells regardless of particle size, with toxicity varying based on dosage.[241]

Achieving precise targeting of ZnO NPs to cancer cells without affecting normal cells remains a significant challenge. It is essential to enhance targeting mechanisms to increase specificity and reduce off-target effects.[242] Furthermore, large-scale synthesis of ZnO NPs with consistent quality and reproducibility is crucial for clinical applications, as variability in NP size, shape, and surface properties can impact their therapeutic efficacy and safety. The regulatory pathway for the approval of nanomedicine, including ZnO NPs, is complex and requires comprehensive evaluation of their safety, efficacy, and quality.[242]

Future research directions should prioritize conducting in-depth toxicological studies to understand the long-term effects of ZnO NPs in vivo, focusing on toxicity mechanisms, biodistribution, and clearance from the body.[243] It is also important to explore advanced surface modification techniques that enhance the stability, targeting specificity, and therapeutic efficacy of ZnO NPs. Functionalizing the surface with targeting ligands, polymers, and other biomolecules can significantly improve their performance.[243]

In addition, investigating the use of ZnO NPs in combination with other treatment modalities, such as immunotherapy, can enhance anticancer efficacy; thus, the synergistic effects with existing treatments should be thoroughly evaluated.[243] Bridging the gap between laboratory research and clinical application through well-designed pre-clinical and clinical studies is critical. These studies should aim to establish safety, optimal dosing, and therapeutic protocols for ZnO NP-based treatments.[243]

Developing personalized nanomedicine strategies that utilize ZnO NPs tailored to individual patient profiles could maximize therapeutic efficacy while minimizing adverse effects.[243] Finally, research into novel synthesis methods to produce ZnO NPs with controlled size, shape, and surface properties should prioritize green synthesis approaches that utilize eco-friendly materials and processes, thereby enhancing biocompatibility and reducing environmental impact.[243]

Targeted NPs offer several therapeutic benefits, such as multidrug conjugation, high payload capacity, adjustable discharge kinetics, selective localization, and the ability to evade multidrug resistance mechanisms.[244] Various NP functionalization approaches have been developed to enhance the selectivity and specificity of anti-cancer activity. For instance, modifying the surface of ZnO NPs has significantly improved their ability to target specific cancer cells and increased their resilience over time. Research has focused on altering of ZnO NP surfaces using various biological elements, including proteins, hyaluronan, nucleic acids, peptides, and folic acid.[232] This biocompatible coating did not affect the anticancer effectiveness of ZnO NPs but also increased their selective targeting of cancer cells while sparing normal cells.[232]

## Anti-Diabetic Activity of ZnO NPs

Research has explored the anti-diabetic effects of ZnO NPs due to their role in facilitating insulin storage, production, and release, given the essential nature of Zn in these processes.[245] Studies have shown that ZnO NPs can significantly increase insulin levels, enhance glucose elimination, and improve Zn status, exhibiting higher anti-diabetic activity than $ZnSO_4$.[245] For instance, Gadoa et al[246] demonstrated that ZnO NPs could restore the cellular structure, improve structural integrity, and normalize biochemical markers such as serum insulin and blood glucose levels, thus proving effective in managing diabetes-induced pancreatic disorders.[246] Further trials combined ZnO NPs with diabetic medications like red sandalwood and vildagliptin to enhance efficacy.[247] These medications inhibit pancreatic amylase and colonic-glucosidase, enzymes that break down carbohydrates into glucose.[248]

Diabetes results from a metabolic imbalance due to inadequate insulin production or effectiveness, leading to inefficient carbohydrate processing and persistently high blood sugar levels.[249] Inhibiting enzymes like glucosidase and amylase can help regulate blood glucose levels. Current drugs can inhibit these enzymes but often have drawbacks.-[250] However, Ci-ZnO NPs have demonstrated promising results in suppressing the activities of amylase and glucosidase by interacting with their active and allosteric sites.[250] This interaction leads to competitive and non-competitive

inhibition, with inhibition percentages ranging between 20–74% for amylase and 36–82% for glucosidase, the latter having a higher inhibition rate.[250]

For glucosidase, ZnO NPs can bind directly to the active site, preventing substrate access, or to allosteric sites, causing conformational changes that reduce enzyme activity.[251] Similarly, for amylase, ZnO NPs can compete with the substrate for the active site or bind allosterically, altering the enzyme's shape and functionality.[251]

These interactions result in structural changes, including alterations in the secondary and tertiary structures of the enzymes, which affect their stability and flexibility, ultimately reducing their catalytic efficiency.[252] Experimental evidence, including spectroscopic and molecular docking studies, supports these mechanisms, demonstrating that ZnO NPs can induce significant conformational alterations and modify the stability of enzyme molecules.[252,253] According to Nazarizadeh and Asri-Rezaie[254], over 400 million people worldwide had diabetes in 2014, making it a significant public health concern. Diabetes mellitus arises from metabolic dysfunction where the body either fails to produce enough insulin or utilizes it ineffectively.[255] Zn plays a crucial role in insulin storage, synthesis, and secretion and is essential for maintaining insulin's structural integrity.[256] ZnO NPs have been developed as a novel method for Zn administration, and their anti-diabetic benefits have been investigated. For example, red sandalwood extract with ZnO NPs were used as an anti-diabetic medication, finding that the combination was more effective in inhibiting pancreatic glucosidase and amylase than the components alone.[233]

In another study, Nazarizadeh and Asri-Rezaie[254] examined $ZnSO_4$ and ZnO NPs' antioxidant activity in diabetic rats, finding that small ZnO NPs had a significantly larger antidiabetic impact at higher doses, demonstrated by decreased blood sugar levels, increased insulin levels, and enhanced serum Zn status. Higher doses also aggravated oxidative stress, indicated by increased malondialdehyde (MDA) production and decreased total antioxidant capacity.[233]

ZnO NPs enhance insulin signaling pathways and intracellular glucose transport primarily by mimicking insulin action and stimulating pancreatic β-cells.[257] They activate the insulin receptor, initiating a signaling cascade that includes the phosphorylation of insulin receptor substrates (IRS), activation of phosphatidylinositol-3-kinase (PI3K), and protein kinase B (Akt).[258] Akt activation promotes the translocation of glucose transporter 4 (GLUT4) to the cell membrane, facilitating increased glucose uptake.[258] In addition, ZnO NPs stimulate β-cells to secrete more insulin and reduce oxidative stress, thereby improving β-cell function and overall glucose homeostasis under diabetic conditions.[259]

Elevated blood sugar levels can enhance inflammation by modulating the production of C-reactive protein (CRP) and interleukins, which are associated with cardiovascular conditions.[249] Rehana et al[249] synthesized ZnO NPs using hydroxyethyl cellulose as a stabilizer to alleviate diabetic complications. These NPs reduced levels of asymmetric dimethylarginine (ADMA), fasting blood sugar, MDA, and inflammatory markers like interleukin-1 (IL-1) and CRP in diabetic rats while increasing nitric oxide (NO) levels and antioxidant enzyme PON-1.[249]

In addition, Eswari et al[260] used leaf extract of teak (*Tectona grandis*) and Indian abutilon (*Abutilon indicum*) to produce ZnO NPs. The X-ray diffraction (XRD) analysis confirmed the effective creation of wurtzite ZnO NPs with average crystalline sizes of 17 nm for teak and 22 nm for Indian abutilon. Optical assessments revealed absorption bands around the 350 nm UV range, indicating band gap values of 3.0 eV and 3.1 eV.[260] The anti-diabetic and anti-inflammatory properties of these ZnO NPs were examined using bovine albumin serum (BSA) denaturation and amylase inhibition techniques, achieving inhibition percentages of 95.42 and 94.82%, respectively.[260] Furthermore, MTT tests indicated a reduction in viability among MCF-7 breast cancer cell lines.[260] In summary, studies suggest that ZnO NPs hold significant potential for treating diabetes and its complications, due to their ability to improve insulin activity, regulate blood glucose levels, and reduce inflammation.

However, several regulatory challenges must be addressed before ZnO NPs can be integrated into clinical practice. Safety concerns, such as potential cytotoxicity and genotoxicity, require thorough assessment, and long-term exposure studies are necessary to ensure safety.[261] Establishing safe and effective dosage ranges is another critical regulatory hurdle.[262] In addition, ensuring consistent quality and reproducibility in the production of ZnO NPs is essential for regulatory approval; thus, detailed characterization including size, shape, surface charge, and coating is necessary for regulatory compliance. Ethical considerations, such as informed consent and long-term monitoring of patients, must also be addressed.[262]

Integrating ZnO NPs into existing diabetes treatment protocols could involve using them as an adjunct therapy alongside current antidiabetic medications, potentially enhancing their effects and reducing required dosages.[263,264] Personalized approaches that consider individual patient responses to ZnO NP therapy could be developed for more effective diabetes management. Furthermore, combining ZnO NPs with other therapeutic agents, such as antioxidants, anti-inflammatory drugs, or insulin sensitizers, may provide synergistic benefits.[265] While ZnO NPs hold significant promise for diabetes treatment, comprehensive research and rigorous regulatory scrutiny are essential to ensure their safe and effective integration into clinical practice.[265]

## Antimicrobial Activity of ZnO NPs

ZnO NPs exhibit promising antibacterial properties due to their substantial surface area and ability to combat various diseases. Recent studies have highlighted their antimicrobial properties, making them a reliable therapeutic option in medical technology at both micro and nanoscale levels.[266–268] Despite their advantages over microparticles, the exact mechanisms underlying their efficacy remain unclear. Notably, ZnO NPs are effective against both Gram-negative and Gram-positive bacteria, as well as spores resistant to high pressure and temperature.[226]

The concentration and size of ZnO NPs significantly impact their pharmacological behavior. The effectiveness of these NPs correlates with the dimensions and quantity, though the precise therapeutic mechanisms are still not fully understood.[269] Some hypotheses suggest that the particle adhesion to microbial surfaces due to constant pressure plays a role, while others propose that the hydrogen peroxide ($H_2O_2$) production is a key factor. Increased dosages of ZnO NPs enhance their potency, treatment time, and efficacy,[269] partly due to variations in particle size and surface area-to-volume ratio.[269]

*Escherichia coli, Vibrio cholerae*, and other Gram-negative bacteria are common models for studying ZnO NPs' antibacterial effectiveness,[270] along with Gram-positive bacteria such as *S. aureus*.[270] Research has also included *Proteus vulgaris, Pseudomonas aeruginosa, B. subtilis*, and *Enterococcus faecalis*.[70] Studies have shown ZnO NPs exhibit significant antibacterial action against these bacteria, often linked to the production of ROS, which disrupt cell membranes and compromise their integrity.[201,271]

In specific studies, ZnO with an average size of around 13 nm disrupted bacterial cell membranes through direct contact, while other findings indicated that Zn(II) ions from ZnO NP suspensions did not exhibit antibacterial effects.[272] For instance, ZnO NPs inhibited *E. coli* at approximately 3.4 mM concentrations and *S. aureus* at concentrations below 1 mM.[272] ZnO NPs have also been studied for their potential in treating cholera, a severe intestinal illness caused by *V. cholerae*.[273] Research by Sarwar et al[274] revealed that ZnO NPs effectively inhibited the growth of the El Tor (N16961) variant of *V. cholerae* by inducing ROS overproduction, leading to bacterial membrane damage and increased permeability. In mouse models, ZnO NPs demonstrated the ability to impede cholera toxin's attachment to the GM1 ganglioside receptor, causing the toxin's structural collapse.[275]

The antibacterial effects of ZnO NPs are believed to stem from their ability to generate oxidative stress, disrupt cell membranes, and impede respiratory enzymes through interaction with Zn(I) ions. This leads to ROS and free radical production, causing irreversible damage to bacterial mitochondria, DNA, and membranes.[226] NPs can penetrate cell membranes more easily than larger particles, allowing direct interaction with intracellular components, which increases ROS production and subsequent cellular damage.[276] The size of NPs also affects their uptake by cells through endocytosis, with smaller ZnO NPs being more readily absorbed and distributed throughout the cytoplasm and organelles, including mitochondria.[277] Once inside, these NPs can cause mitochondrial dysfunction, leading to further ROS production and triggering cell death pathways such as apoptosis or necrosis.[277,278] The primary mechanism of ZnO NPs toxicity is oxidative stress induced by ROS, with smaller NPs generating higher levels of ROS, overwhelming the cell's antioxidant defenses.[277] This imbalance causes oxidative damage to lipids, proteins, and DNA.[277]

Elevated ROS levels can also activate inflammatory pathways. Due to their enhanced ROS production, smaller ZnO NPs provoke stronger inflammatory responses, leading to the release of pro-inflammatory cytokines.[279] Chronic inflammation can result in tissue damage and contribute to diseases, such as cancer. Furthermore, the ROS generated by smaller ZnO NPs can induce DNA damage, leading to mutations and chromosomal aberrations.[280] This genotoxicity may result in cell cycle arrest, apoptosis, or uncontrolled cell proliferation, all of which contribute to carcinogenesis.[280]

In summary, the toxicity of ZnO NPs is strongly influenced by their size. Smaller NPs, with their higher surface area-to-volume ratio, produce more ROS, leading to increased oxidative stress, cellular damage, and inflammation.[64] Understanding these size-dependent effects is crucial for evaluating the safety of ZnO NPs in biomedical and industrial applications. Strategies to mitigate their toxicity may include controlling particle size, surface modifications, or using antioxidants to neutralize ROS.

Studies by Ghasemi and Jalal[281] indicated that ZnO NPs enhance the effectiveness of antibiotics like ceftazidime and ciprofloxacin against *Acinetobacter baumannii*, a pathogen responsible for infections such as pneumonia and meningitis.[281] When combined with antibiotics, improved antibiotic absorption and altered bacterial shape, demonstrating the potential for combined treatments.[282] ZnO NPs also enhance the antibacterial efficacy of the photosensitizer crystal violet.[99,283] Research by Chen et al[284] using surface enhanced Raman spectroscopy (SERS) showed that ZnO NPs antibacterial activity varies with dosage and duration, with smaller doses over extended periods mimicking the effects of higher doses.[284] The effectiveness of ZnO NPs as antibacterial agents is illustrated in Figure 3.

In summary, ZnO NPs possess significant antibacterial properties, and hold promises for various medical and industrial applications. Their dual functionality, including the ability to induce oxidative stress and disrupt cell membranes, makes them potent antibacterial agents suitable for future research and development in combating bacterial infections.

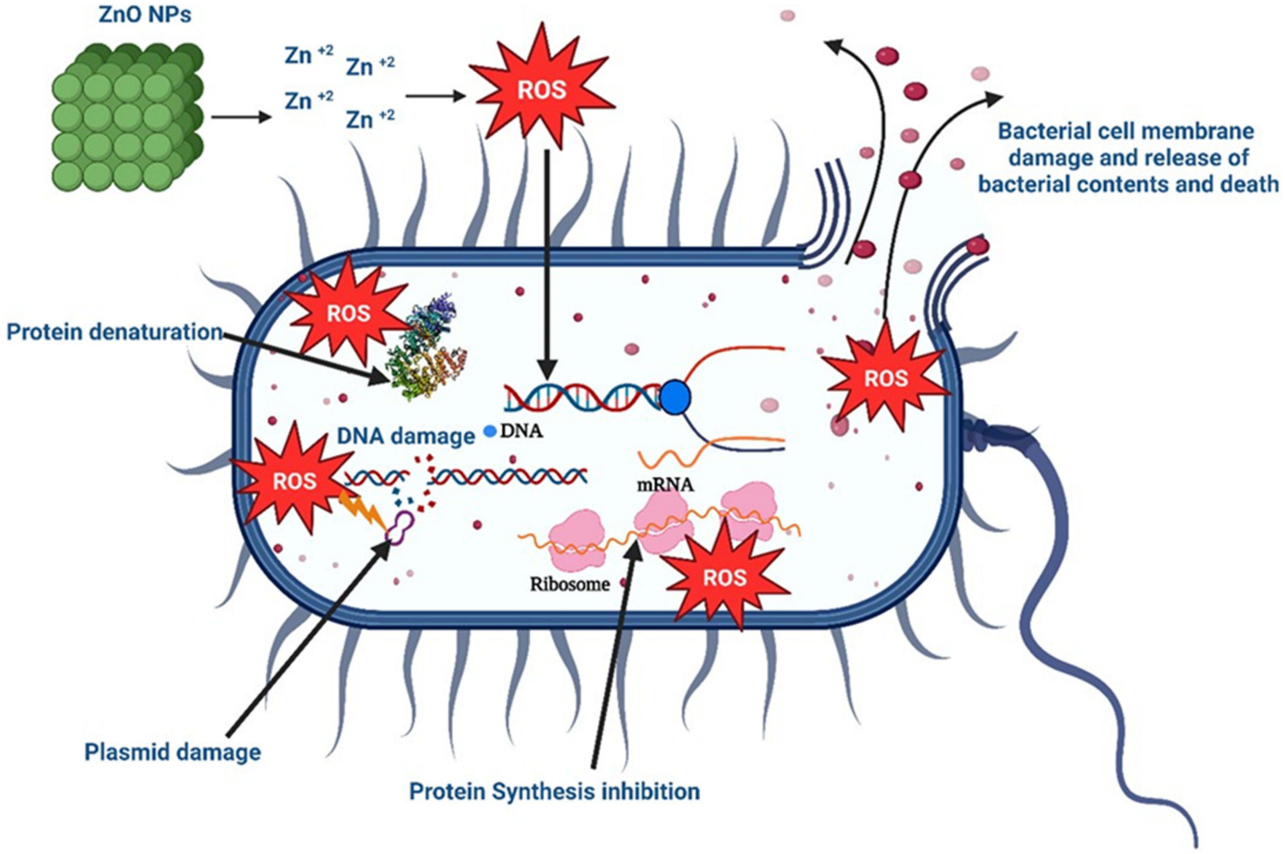


**Figure 3** The antibacterial activity of ZnO NPs.
**Abbreviations**: ZnO NPs, zinc oxide nanoparticles; ROS, reactive oxygen species.

## Impact on NPs Modifications on Cellular Uptake and Targeted Interactions with Cancerous Vs Normal Cells

Modifications to NPs significantly influence their cellular uptake and interactions with both cancerous and normal cells.[276] These modifications can be optimized to improve targeting, minimize side effects, and enhance therapeutic efficacy.[285] Surface modifications play a crucial role in this process. Surface modifications are key, especially when functionalization with targeting ligands such as antibodies, peptides like arginine-glycine-aspartic acid (RGD), aptamers, or small molecules like folic acid. These enable precise targeting of specific antigens overexpressed on cancer cells.[285] For instance, HER2 in breast cancer can be targeted with antibodies, while integrins on tumor vasculature can be targeted with RGD peptides.[286] Aptamers, which are single-stranded DNA or RNA molecules, bind to specific proteins on cancer cells, and folic acid-conjugated NPs can target folate receptors commonly overexpressed in cancer cells.[287]

The surface charge of NPs also influences their interaction with cells. Cationic NPs, which are positively charged, interact more readily with the negatively charged cell membranes, enhancing uptake, but may also increase toxicity.[288] In contrast, anionic and neutral NPs tend to be less toxic and can be modified with stealth properties, such as PEGylation (attachment of PEG) to evade the immune system and increase circulation time.[288,289] The hydrophilicity or hydrophobicity of NP coatings is also crucial; hydrophilic coatings like PEG reduce opsonization and immune recognition[290], while hydrophobic coatings enhance interaction with cell membranes but may result in rapid clearance from the bloodstream.[291]

NPs interaction with cellular receptors is another critical factor. Cancer cells often overexpress receptors, such as transferrin or folate receptors, which can be targeted by corresponding ligands on NPs.[292] Mutated receptors in cancer cells present novel targets that normal cells do not have, enabling selective targeting. Normal cells, with tightly regulated receptor expression, provide an opportunity to design NPs that minimize off-target effects by focusing on receptors overexpressed in cancer cells.[292]

NPs uptake occurs through various cellular pathways. Endocytosis, including clathrin-mediated (CME), caveolae-mediated (CavME), and macropinocytosis, is a primary mechanism for internalization.[293] In CME, NPs bind to receptors that cluster into clathrin-coated pits, leading to internalization. CavME involves internalization through caveolin-enriched plasma membrane invaginations, while macropinocytosis allows larger particles or aggregates to be taken up by membrane ruffling and engulfment.[294] Small and lipophilic NPs can also passively diffuse through the cell membrane without receptor-mediation.[294]

Cancerous and normal cells differ significantly in how they interact with and uptake NPs. The enhanced permeability and retention (EPR) effect, characterized by leaky vasculature and poor lymphatic drainage in tumors, allows for passive NP targeting, a feature typically absent in normal tissues.[295,296] Tumors also have an acidic microenvironment and higher redox potential compared to normal tissues, which supports the use of pH-sensitive and redox-sensitive NPs for targeted release within the tumor.[297] Moreover, hypoxic conditions and the metabolic reprogramming (Warburg effect) in tumors provide further strategies for targeting hypoxia-sensitive and metabolically tuned NPs.[298]

## The Multifaceted Antimicrobial Mechanisms of ZnO NPs

Next-generation nano-antibiotics using ZnO NPs have been developed to combat drug resistance in various treatments.[299] These NPs are distinct in their size, crystalline structure, porosity, shape, and content,[239] which confer broad antibacterial action against a range of pathogens, including *P. aeruginosa, S. aureus*, and *E. coli*.[137]

In both clinical and non-clinical settings, ZnO NPs can be combined with antibiotics and anti-inflammatory drugs to enhance their effectiveness against harmful microorganisms, while reducing the risk of antibiotic resistance.[137,138] Despite the unclear specific mechanisms of their medicinal activity, ZnO is being explored as a pharmacological agent at micro- and nanoscale levels. It is suggested that cell swelling occurs primarily due to ROS generation on particle surfaces, Zn ion release, membrane dysfunction, and NP uptake.[300] High temperature processing of ZnO NPs significantly affects their therapeutic efficacy, whereas lower temperature processing has a lesser effect.[300] ZnO NPs are also being studied in conjunction with medical ablation techniques and their potential in anti-cancer treatments when exposed to heat.[301]

ZnO materials exhibit antimicrobial effects through several mechanisms, including the release of Zn(II) ions, adsorption abilities, ROS generation, reactions within microorganisms, induction of lipid peroxidation, interference with DNA

replication, and DNA fragmentation,[302] Zn(II) ions produced by ZnO NPs/microparticles (MPs) affect metabolic processes and enzyme systems in microorganisms, inducing antibacterial responses.[159] Under UV and visible light, ZnO NPs/MPs act as photocatalysts, generating ROS and attracting particles to the bio-membrane through charge interactions.[303,304]

Furthermore, ZnO NPs can release Zn(II) ions, which interact with the bacterial cell membrane and intracellular components.[305,306] These ions bind to negatively charged membrane sites, disrupting membrane potential and inhibiting vital functions like nutrient transport and energy production.[305] In addition, ZnO NPs and Zn(II) ions interfere with cellular respiration by inhibiting respiratory enzymes essential for the electron transport chain, leading to reduced ATP production and energy depletion.[307,308] Furthermore, ROS generated by ZnO NPs oxidize proteins, disrupting metabolic enzymes and structural proteins crucial for cell integrity.[283] ROS can also induce DNA strand breaks, resulting in mutations and impaired replication and transcription.[129]

ZnO NPs/MPs interact with microorganisms by adsorbing onto their positively charged surfaces and negatively charged cell walls or bio-membranes.[309] Their penetration into the membrane causes physical damage, creating pits and perforations that compromise its integrity, leading to leakage and cell death.[310] They also mediate lipid peroxidation-induced oxidative stress, which damages DNA. The effectiveness of ZnO NPs/MPs against pathogenic microorganisms varies depending on their porosity, particle size, and shape.[309,310]

ZnO NPs/MPs exhibit enhanced antibacterial action even against deadly pathogens and show broad antibacterial properties when combined with other antibiotics. This adaptability makes them promising platforms for commercial and clinical applications. Other biomaterials, metal doping, and metal oxide NPs/MPs are also being explored for similar purposes.[302]

ZnO NPs are not only effective against bacteria but also against fungi, as shown in Figure 4. Abd-Elmaqsoud et al[311] found that ZnO NPs derived from *Moringa oleifera* were detrimental to the plant pathogens, *Alternaria saloni* and *Sclerrotium rolfii*. Similarly, Alhazmi and Sharaf[312] explored the effectiveness of ZnO NPs against various fungal strains,

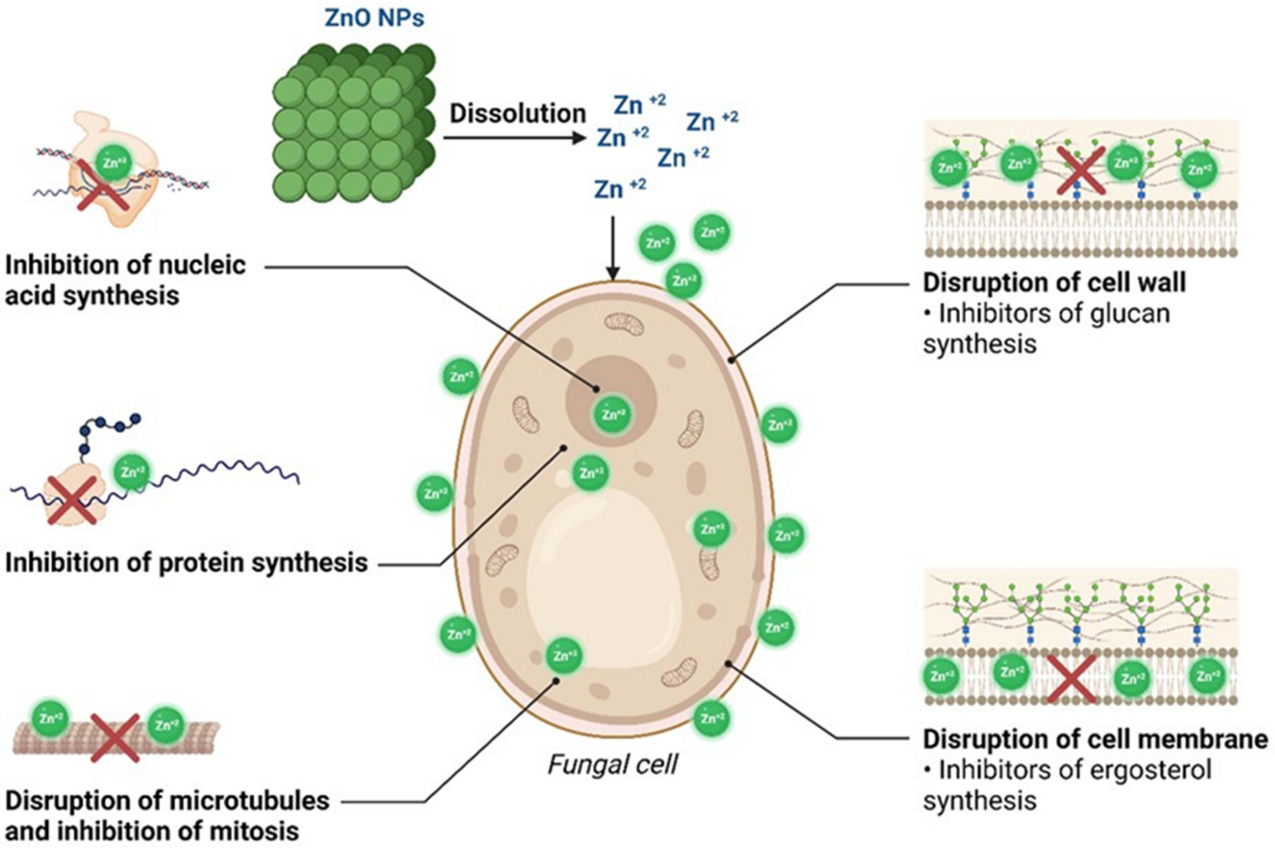


**Figure 4** The antifungal activity of ZnO NPs.
**Abbreviation**: ZnO NPs, zinc oxide nanoparticles.

noting significant impact on both plant and food pathogens, particularly *Aspergillus nidulans, Trichoderma harzianum, Rhizopus stoloniferous*, and *Aspergillus flavus*. Consequently, the researchers suggested that ZnO NPs could be utilized in the food and agriculture industries.[312] In addition, ZnO NPs exhibit a concentration-dependent effect on the survival of *Candida albicans*. At a concentration of 0.1 mg/mL, ZnO NPs significantly reduced *C. albicans* viability. When combined with visible light, the frequency of yeast cell death increased.[312]

Perveen et al[313] produced ZnO NPs using vegetable seed extracts from Brassicaceae plants, including sarson, turnip, white radish, red radish, and cauliflower. These ZnO NPs demonstrated antibacterial activity, with inhibition zones ranging between 10–20 mm, compared to 25 mm for streptomycin.[313] This indicates that red radish, white radish, turnip, sarson, and cauliflower can be sources of ZnO NPs with active antibacterial properties.[313]

The response of bacterial and fungal cell membranes to ZnO NPs differ due to their distinct membrane compositions. In bacterial cells, ZnO NPs primarily disrupt the membrane and increase permeability through electrostatic interactions between the negatively charged membrane components and the positively charged ZnO NPs.[314,315] This is further intensified by the generation of ROS, which exacerbates membrane damage, leading to cell lysis and death. In contrast, fungal membranes, rich in sterols like ergosterol, respond to ZnO NPs by increasing membrane permeability and causing cellular contents leakage.[316] Although ROS generation also contributes to membrane damage in fungi, the effect is less pronounced due to their stronger antioxidative defenses compared to bacteria.[316]

## Anti-Inflammatory Activity of ZnO NPs

Inflammation is a complex response of body tissues to various potential threats, including irritants, cellular damage, or pathogens.[317] The biological functions of Zn ions and the creation of NPs have highlighted the anti-inflammatory capabilities of ZnO NPs. Atopic dermatitis (AD), a chronic inflammatory skin disorder, is characterized by a decreased skin barrier function and a complex interaction between genetic and environmental factors.[317]

Textiles, which are in close contact with the skin, have been explored for their potential therapeutic effects. Kahru and Mortimer[318] investigated the impact of ZnO-enhanced textile fibers on oxidative stress in individuals with AD. Their results indicated that wearing ZnO-induced fabrics overnight for three consecutive days significantly improved pruritus and sleep quality, likely due to the antibacterial and antioxidant properties of ZnO fabrics.[318]

Youssef et al[232] studied the effect of ZnO NPs of varying sizes on allergic skin in a mouse model of AD. They found that the bulk-sized ZnO (bZnO) remained on the skin's surface layers, while nanoscale ZnO (nZnO) could penetrate the deeper layers of sensitive skin prone to allergic reactions..[232] In an animal model of Alzheimer's disease, nZnO significantly decreased pro-inflammatory cytokines and exerted greater anti-inflammatory effects than bZnO, as evidenced by reductions in Th2 cytokines, IL-13, IFN-, and IL-10.[232] Such findings demonstrate that ZnO NPs significantly reduce skin inflammation in AD models.

These interactions primarily occur through the inhibition of key inflammatory signaling pathways. ZnO NPs are taken up by immune cells through endocytosis, where they release Zn ions into the cellular environment.[319] These ions disrupt signaling cascades that lead to cytokine production, specifically by reducing the activation of nuclear factor-kappa B (NF-kB), a critical transcription factor involved in pro-inflammatory cytokine expression.[213]

The NF-κB signaling pathway plays a central role in regulating inflammation and immune responses.[320] Normally, NF-κB is kept inactive in the cytoplasm by inhibitor proteins (IκBs).[320] Upon activation by pathogens or inflammatory signals, IκB are phosphorylated and degraded, allowing NF-κB to move into the nucleus and trigger the transcription of target genes, including IL-6 and TNF-α.[320,321] ZnO NPs inhibit this process by two main mechanisms: First, Zn ions prevent IκB phosphorylation and degradation, thereby blocking NF-κB activation.[213] Second, ZnO NPs scavenge ROS, which are involved in NF-κB activation.[322] By reducing ROS levels and oxidative stress, ZnO NPs further inhibit NF-κB activation, leading to lower transcription of pro-inflammatory cytokines and reduced inflammation. This modulation of the NF-κB pathway by ZnO NPs highlights their potential as therapeutic agents in controlling inflammation and related diseases.[322]

The anti-inflammatory capabilities of ZnO NPs extend beyond AD, proving effective for various inflammatory diseases. Imraish et al[323] assessed the anti-inflammatory potential of ZnO NPs on RAW 264.7 macrophages stimulated by LPS, noting their superior ability to decrease NO production and suppress the expression of associated proteins such as inducible NO synthase (iNOS), COX-2, IL-1, IL-6, and TNF in a dose-dependent manner.[323] This study highlights the broad spectrum of anti-inflammatory effects of ZnO NPs, emphasizing their potential therapeutic applications in various inflammatory conditions.[323]

Further supporting the anti-inflammatory role of ZnO NPs, Abdelbaky and colleagues[324] synthesized ZnO NPs using a solution of *Pelargonium odoratissimum* leaf extract as a reducing agent.[324] In vitro models using the human red blood cells (HRBC) membrane stabilization method (MSM), such as hypotonicity-induced hemolysis, were employed to assess the anti-inflammatory properties of both the ZnO NPs and the water-based extract from *P. odoratissimum* leaves.[324] Compared to conventional indomethacin at a dose of 1000 µg/mL, a maximum membrane stabilization of 95.6% was observed.[324]

The effectiveness of bulk and nano-ZnO was examined, revealing that only nano-sized ZnO particles can infiltrate the innermost layers of allergic skin, reducing localized skin irritation while promoting the synthesis of IgE antibodies. Ilves et al[157] hypothesized that this is due to non-specific processes caused by liberated Zn (II) that limit B-cell IgE synthesis. These findings suggest that ZnO NPs could potentially be used to treat inflammation. The anti-inflammatory impact of ZnO NPs is illustrated in Figure 5.

## Treatment of Skin Disorders Using ZnO NPs

ZnO is commonly found in medications such as diaper rash powders, barrier creams, antimicrobial ointments, hemimorphite cream, and antidandruff shampoos. Athletes also use ZnO tape to protect soft tissue during exercise.[232] Incorporating ZnO NPs into creams, ointments, and lotions provides protection against sunburn and other UV-related skin issues. Due to its excellent UV-A (320–400 nm) and UV-B (280–320 nm) reflectance and perfect photostability, the Bureau has officially approved ZnO for use in sunscreen.[232]

Studies have shown that ZnO NPs can downregulate type I collagen in skin tissue. Results indicate that ZnO NPs creams at low (1%) and high (6%) concentrations offer preventive benefits against oxidative damage and allergic dermatitis induced by lead oxide, likely due to the anti-inflammatory and antioxidant properties of ZnO NPs.[325] At

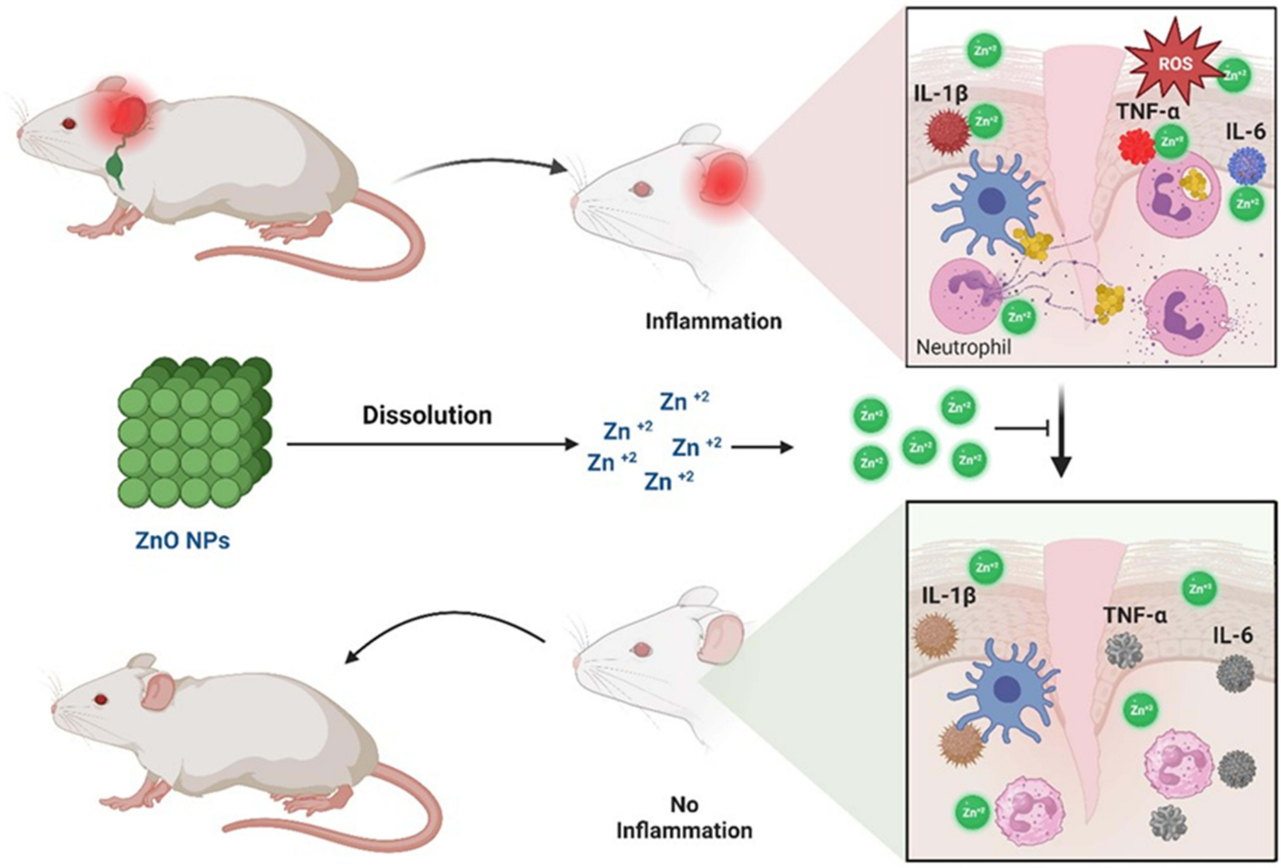


**Figure 5** Anti-inflammatory effect of ZnO NPs.
**Abbreviations**: ZnO NPs, zinc oxide nanoparticles; ROS, reactive oxygen species.

lower concentrations, such as 1%, ZnO NPs can effectively reduce inflammation and oxidative stress, promoting skin health and providing a barrier against environmental pollutants.[326] The antioxidant properties neutralize free radicals, reducing oxidative damage to the skin. In addition, their anti-inflammatory effects can mitigate allergic responses and dermatitis by decreasing the production of pro-inflammatory cytokines like IL-6 and TNF-α.[327]

Conversely, higher concentrations of ZnO NPs, such as 6%, while still offering protection against oxidative stress and inflammation, may pose risks with frequent and prolonged exposure.[326] Research shows that in cases of epidermal barrier dysfunction, such as eczema or psoriasis, high concentrations of ZnO NPs increase the risk of adverse effects, including melanoma.[322] In mouse models with epidermal barrier failure, topical application of ZnO NPs led to penetration into deeper skin layers, reaching the stratum basale, causing skin lesions resembling melanoma.[322] This suggests that high doses of ZnO NPs can disrupt normal cellular functions when the skin barrier is compromised.

Furthermore, both in vitro and in vivo studies have shown that ZnO NPs can exert anti-apoptotic effects on melanocytes by activating the NF-κB pathway through oxidative stress, leading to increased cell survival and proliferation.[322] In compromised skin, this could contribute to malignancies like melanoma.[322]

The distinction between the effects of different ZnO NP concentrations highlights the importance of dosage. While low concentrations primarily offer protective and benefits by reducing oxidative damage and inflammation, high concentrations can pose significant risks, especially in compromised skin conditions.[326] The ability of ZnO NPs to penetrate deeper skin layers and activate pathways that prevent apoptosis and promote cell proliferation highlights the need for careful consideration of concentration and exposure duration. Balancing the benefits and risks of ZnO NPs is crucial, particularly in therapeutic and cosmetic applications where long-term skin health is a priority.[322,326] The skin-protecting impacts of ZnO NPs are displayed in Figure 6.

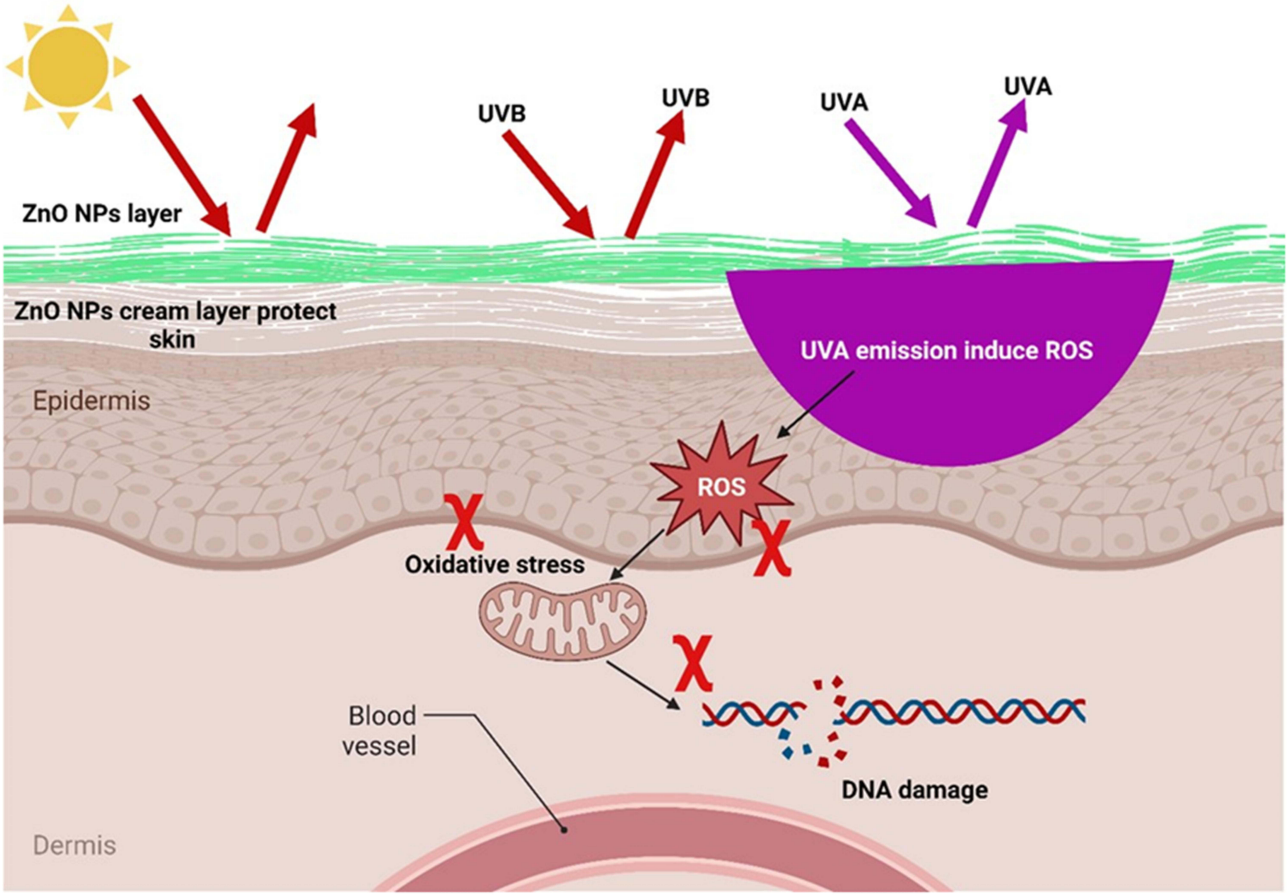


**Figure 6** Skin protective effect of ZnO NPs.
**Abbreviations**: ZnO NPs, zinc oxide nanoparticles; ROS, reactive oxygen species; UV, ultraviolet.

## ZnO NPs and Drug Delivery

Nanotechnology has numerous applications, one of the most important being drug delivery, which has proven effective in treating various diseases, including cancer.[328–330] NPs are crucial in medication transportation.[221] Many researchers have utilized ZnO NPs for drug delivery across different diseases.[181] For instance, Badıllı et al[331] employed ZnO quantum dots (QDs) to deliver DOX precisely to HeLa cells. To enhance the stability of these nanomaterials, chitosan was applied to ZnO NPs.[181] Their research demonstrated that this drug delivery technology could successfully transport DOX to cancer cells.[181] In addition, NPs are significant in gene delivery methods for various cells, particularly malignant cells.[181] This gene transfer method offers several advantages, including the effective and secure delivery plasmid-containing genes to target tissues.[181]

The differences between drug and gene delivery using NPs are significant in terms of mechanisms, requirements, and necessary modifications to ensure efficacy and stability within the body.[332] In drug delivery, NPs act as carriers for therapeutic agents like DOX, enabling targeted and controlled release.[333] The primary goal is to enhance the drug's solubility, stability, and bioavailability while minimizing side effects.[332,333] For instance, ZnO NPs used for DOX delivery can be modified with chitosan, which not only improves stability but also enhances cellular uptake and controlled release at the target site, ensuring efficient delivery to cancer cells.[333]

In contrast, gene delivery involves transporting genetic material, such as DNA or RNA, into cells to modify gene expression and treat diseases at the genetic level.[334] NPs in gene delivery must protect the genetic material from degradation by nucleases and facilitate its entry into target cells.[334,335] Common modifications include adding cationic polymers or lipids to form complexes with negatively charged nucleic acids, protecting them from enzymatic degradation and promoting cellular uptake.[336,337] For example, coating NPs with chitosan enhances their ability to bind with DNA or RNA and facilitates endocytosis by target cells.[338]

Stability within the body is crucial for both drug and gene delivery systems.[339] For drug delivery, NPs are often modified with biocompatible and biodegradable materials to prevent premature degradation and ensure sustained release of the therapeutic agent.[339–341] In gene delivery, stability is enhanced through protective coatings and stabilizing agents that shield the genetic material from the biological environment.[342] In addition, targeting ligands can be attached to the surface of NPs to direct them to specific cell types, improving the efficiency of gene transfer and reducing off-target effects.[342]

## Bio-Imaging and ZnO NPs

This method of gene dispersion has several advantages. Genes generated on the surface of NPs encoded by plasmids can be safely and efficiently transferred to target tissues.[343,344] Recent research has explored ZnO nanostructures such as, nanorings, nanorods, nanotubes, and NPs, particularly for their potential in biological imaging.[344] This characteristic has several biological and therapeutic uses and applies to varied degrees.[344] Luminescent ZnO NPs, also known as ZnO QDs, possess advantageous photophysical properties and are widely recognized for their safety.[344] ZnO is used as a food preservative and a component in sunscreen products, making its luminescent properties applicable in various natural and medicinal contexts.[344] ZnO is used as fluorescence imaging often used in preclinical research due to its cost-effectiveness and practicability, benefits from these properties.[249]

Several studies have highlighted the importance of ZnO NPs in cellular imaging. These NPs can emit green fluorescence due to oxygen vacancies and other processes, facilitating the visualization of cancer cells via minimally invasive methods.[344] Green, fluorescent ZnO NPs conjugated with transferrin have been used for this purpose. Additionally, the optical properties of ZnO nanomaterials can be modified by incorporating cations like Ni, Cu, or Co, stabilized in aqueous colloidal solutions for various imaging purposes.[344] These small ZnO NPs can infiltrate the cell nucleus, and hetero-structural ZnO/Au nanocomposites have been developed and studied for their optical properties and biocompatibility.[344]

ZnO nanorods can form Au nanoclusters on their tips and surfaces. ZnO nanorods coated with antibodies against the epidermal growth factor receptor have been used to scan cancer cells in vitro.[318] QDs are favored for optical imaging due to their attractive optical characteristics.[345] ZnO QDs used in in vitro cell imaging showed stable luminescence without cytotoxicity under UV illumination. These QDs have also been evaluated in mice through intradermal and intravenous injections.[209]

Each imaging method has its own advantages and disadvantages.[346] Functionalizing nanomaterials to be detectable by multiple imaging modalities offers synergistic benefits.[346] Nanomaterials are more suitable for multimodal imaging than small molecules due to their larger surface areas, providing more sites for functionalization and allowing customization for multimodal detection.[347] For instance, sub-6 nm-diameter Gd-doped ZnO QDs have been generated for optical and magnetic resonance imaging (MRI). $Fe_3O_4$-ZnO core-shell magnetic QDs have also been investigated for potential cancer imaging and therapy.[348]

In clinical settings, radionuclide-based imaging techniques like PET and single-photon emission computed tomography (SPECT) are more frequently than optical imaging due to their unlimited tissue penetration, high sensitivity, and quantitative capabilities.[346,348] Recent studies have shown that ZnO NPs available in various morphologies, can be used as bioimaging materials.[349] Hyperbranched polymers have been employed to produce amphibious ZnO QDs with blue fluorescence, demonstrating their bioimaging applicability.[349] ZnO NP surfaces are easily modifiable and durable in aqueous solutions, with water-soluble ZnO enhanced by hyperbranched polyethylenimine compounds performing well in bioimaging.[349]

Masar et al[350] investigated pure n-type ZnO NPs for bioimaging using standard fluorescence microscopy methods. Typically, NPs require UV excitation sources to emit light. However, this study shows that by reducing the energy gap, a 405 nm laser may sufficiently excite NPs for emissions observable during confocal microscope live-cell imaging.[350] This research lays the foundation for using these NPs in various bioimaging applications, allowing to study interactions between pristine n-type ZnO NPs and human cells using fluorescence-driven imaging techniques.[351] Their developing production process also controls specific defects in pure n-type ZnO NPs for bioimaging.[351]

## ZnO NPs Based Biosensors

Biosensors have broad applications in various fields, including the food industry, healthcare, environmental monitoring, and biological or chemical assessment.[352] They are classified based on their detection principles into electrochemical, photometric, piezoelectric, and calorimetric devices.[352] Nanomaterials are gaining significant attention due to their unique features, whether used alone or in conjunction with biologically active substances.[353] These properties make them a robust foundation for designing high-performance biosensors. The expanded surface area of nanomaterials facilitates the attachment of a wide range of biomolecules, such as antibodies, enzymes, and other proteins.[353] Additionally, they enable direct electron transfer from the electrodes to the active regions of the biomolecules.[353]

ZnO nanomaterials, in particular, have several desirable properties, including high isoelectric point (IEP; 9.5), strong adsorption capacity, excellent biosensing, and high catalytic efficiency.[156] These properties make ZnO suitable for electrostatic adsorption of specific proteins like enzymes and antibodies, which have lower IEPs.[156] Nanomaterials with higher electron transfer capacities, larger surface areas, and improved biocompatibility or stability are especially beneficial for use in biosensors.[354] ZnO-based biosensors are commonly used to detect various small-molecule analytes, such as cholesterol, glucose, $H_2O_2$, phenol, and urea. There are numerous biosensors available for detecting specific chemical and physical properties, like pH.[355]

Dönmez[356] created an amperometric glucose biosensor employing ZnO NPs and the root of *Zingiber officinale*. Glucose oxidase (GOx) was anchored onto a carbon paste electrode (CPE) modified with ZnO through glutaraldehyde cross-linking.[298] The resulting biosensor (GOx-ZnO/CPE) demonstrated excellent electrocatalytic glucose measurement capabilities. It featured a low detection limit (14.7 uM), rapid response time (less than 1 second), high sensitivity (15.98 $A/mM.cm^2$), and high biological affinity (Michaelis-Menten constant of 0.99 mM). Additionally, the biosensor showed excellent resistance to interference from uric and ascorbic acids.[298]

The large surface area and excellent electronic transport properties of ZnO NPs significantly enhance sensor sensitivity by providing more active sites for biomolecule attachment and facilitating efficient electron transfer.[348,357] The increased surface area allows for greater adsorption of biomolecules such as enzymes, antibodies, and proteins, improving the chances of interactions with target analytes.[358] These interactions are essential for detection, as they enhance the binding affinity and specificity of the sensor.[358] In addition, ZnO NPs enable direct electron transfer between the biomolecules and the electrode, leading to faster and more accurate responses.[357,358] Together, these combined properties make ZnO NPs highly effective in developing sensitive and reliable biosensors.[358]

## Toxicological Effects of ZnO NPs

The release of Zn-ions from ZnO NPs highlights their potentially hazardous nature, despite being typically considered insoluble in water.[359] The pathways through which NPs are taken up by cells influence their surface, shape, size, and properties.[359] Enhanced understanding of NP toxicity in both environmental and biological contexts has prompted nanotoxicologists to call for deeper insights into the atomic interactions between NPs and organic structures.[359]

Aravantinou et al[345] investigated the enduring harmful effects of ZnO NPs on microalgae within a reconstructed traditional water treatment setup, incorporating a continuous provision of NPs. Like other metal oxide NPs, ZnO NPs are known for generating ROS and cause apoptosis, in addition to their extraordinary healing capabilities. Due to their properties, ZnO NPs serve as antimicrobial, antibacterial, and anticancer agents.[345] They have been shown to produce synergistic benefits when used with various therapy regimens. ZnO NPs are employed for clinical diagnostics and targeted medicine administration, having several applications in the medical field and being environmentally safe.[345] Additionally, they are economically viable as they are inexpensive to produce.[345]

Furthermore, ZnO NPs exhibit differential effects on cancerous versus healthy cells, which is crucial for their safe therapeutic use. In cancerous cells, ZnO NPs induce oxidative stress and apoptosis more effectively due to increased ROS production and an altered redox state.[19,360] This targeted effect enhances their potential as anticancer agents. In contrast, healthy cells are generally more resilient to oxidative stress and less susceptible to ZnO NP-induced toxicity.[361] However, high concentrations or prolonged exposure can still harm healthy cells, potentially causing inflammation or cellular damage.[362] Therefore, precise dosage and targeted delivery are essential to optimize therapeutic benefits while minimizing toxicity risks to healthy tissues.[362]

# Challenges and Future Perspectives

The green synthesis of ZnO NPs faces several challenges that must be overcome for effective biomedical application. A key issue is the variability in biological sources.[342] The biochemical compositions of plants, microorganisms, and algae varies significantly, which affects the size, shape, and functionality of the resulting NPs.[342] This inconsistency complicates standardization, which is essential for ensuring consistent quality in biomedical applications.[342] In addition, scaling up green synthesis from laboratory settings to industrial production remains a significant obstacle.[363]

Another challenge is the limited understanding of the biochemical mechanisms involved in reducing and stabilizing metal ions through biological agents.[359] This knowledge gap makes it difficult to control and optimize the synthesis process, resulting in issues with reproducibility and NP uniformity.[359]

Regulatory and safety concerns further complicate the application of green synthesis in biomedicine. Although eco-friendly, these methods still require extensive testing for toxicity, biocompatibility, and long-term safety to gain regulatory approval.[172] The regulatory landscape for nanomaterials is continually evolving with stringent safety standards necessary for clinical and commercial use.[172] Additionally, the cost-effectiveness of green synthesis relies on the availability and accessibility of biological sources.[364] Seasonal variations and geographical limitations can impact the supply of raw materials, affecting production and cost.[364]

Despite these challenges, the future of green synthesis of ZnO NPs is promising. Advancements in characterization techniques, such as high-resolution transmission electron microscopy (HRTEM), X-ray diffraction (XRD), and Fourier-transform infrared spectroscopy (FTIR) are offering deeper insights into the mechanisms of synthesis.[365] These tools enable better control over NP production by revealing the interactions between metal ions and biological molecules. Furthermore, integrating green synthesis methods with other eco-friendly technologies like renewable energy sources and biodegradable materials can enhance the sustainability and environmental benefits of ZnO NP production, contributing to a more sustainable nanotechnology industry.[342]

Functionalizing ZnO NPs with specific biomolecules, ligands, or polymers could enhance targeted delivery in biomedical applications, leading to improved drug delivery systems, better imaging techniques, and more effective therapies.[366] Exploring a wider variety of biological sources, such as rare plants, extremophiles, and marine organisms, could also open new avenues for green synthesis of NPs with unique and desirable properties.[367]

Interdisciplinary collaboration among material scientists, biologists, chemists, and engineers will be critical in overcoming these challenges. Such partnerships can drive innovation and optimize green synthesis methods. Finally, developing comprehensive regulatory frameworks specific to nanomaterials can ensure the safe and sustainable production of ZnO NPs, with clear guidelines to safeguard both environmental and human health.

## Conclusion

The green synthesis of ZnO NPs represents a major advancement in biomedical nanotechnology. Over the past decade, their unique properties have been widely explored, particularly in antibacterial treatments, drug and gene delivery, anticancer therapies, cell imaging, and biosensing. While traditional synthetic methods are effective, they pose significant economic and environmental challenges. In contrast, green synthesis method, using plants, plant extracts, and microorganisms, offers a sustainable and eco-friendly alternative that reduces environmental impact, lowers production costs, and minimizes health risks, making it suitable for large-scale production.

Green synthesis harnesses the natural biochemical processes of biological agents, such as plant-derived compounds, to reduce metal ions and stabilize NPs. This method not only adheres to green chemistry principles but also enhances the biocompatibility and therapeutic potential of ZnO NPs. Recent studies emphasize the superior antibacterial and anticancer properties of ZnO NPs produced via green synthesis, highlighting their potential in medical and pharmaceutical applications.

However, several challenges remain before the full benefits of green synthesis can be realized. These include variability in biological sources, difficulties in scaling up production, limited understanding of the underlying biochemical mechanisms, stability concerns, and regulatory barriers. Overcoming these hurdles will require advancements in characterization techniques, integration of green synthesis with other sustainable technologies, and interdisciplinary research efforts. Establishing comprehensive regulatory frameworks is essential for ensuring the safe and effective use of ZnO NPs in biomedical applications.

Despite these obstacles, the future of green synthesis for ZnO NPs is promising. Improved characterization methods, such as HRTEM and FTIR, can provide deeper insights into synthesis mechanisms and better control over production. Functionalizing ZnO NPs with specific biomolecules or polymers can enhance their targeted delivery and therapeutic effectiveness. In addition, exploring a broader range of biological sources may reveal unique properties for NP synthesis. This review highlights the potential of green synthesis to revolutionize nanotechnology, providing eco-friendly, cost-effective solutions that align with global sustainability goals.

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## Disclosure

The authors report no conflict of interest in this work.

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