Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 8 Issue 6 June 2024

Mini Review

# Recent advances in Green Synthesis and Therapeutic Potential of Zinc Oxide Nanoparticles: Characteristics and Applications

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**Received:** April 30, 2024

**Published:** May 06, 2024

## Abstract

The development of antibiotic resistance in bacteria is one of the most pressing problems faced by the world. One of the promising ways that have been discovered to overcome microbial resistance to antibiotics is the use of metal nanoparticles and their oxides. In particular, numerous studies have shown the high antibacterial potential of zinc oxide nanoparticles (ZnO-NPs) in relation to gram-positive and gram-negative bacteria (*E. coli* and *S. aureus*) and many other Multi Drug Resistant Bacteria (MDR).This literature review is focused on the synthesis, effects, and antimicrobial properties of ZnO-NPs along with its recent use as a potential therapeutic agent in treating various diseases by inhibiting the causative microorganisms. It also includes an analysis of the results of studies in recent years aimed at studying the potential of nanoparticles based on zinc oxide and various ways to increase the antibacterial efficiency. It is also observed that the combination of ZnONPs with other materials causes a synergistic effect which increases the efficacy of the nanoparticle due to the change in its antimicrobial properties.

**Keywords:** Zinc Oxide Nanoparticles; Green Synthesis; Characteristics; Therapeutic Applications

## Graphical abstract

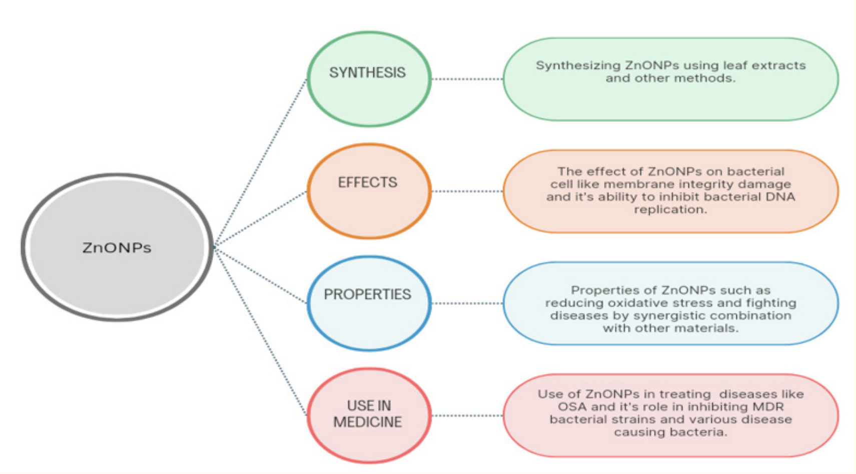


**Figure a**

**Citation:** PL Akshaya and Saranya R. "Recent advances in Green Synthesis and Therapeutic Potential of Zinc Oxide Nanoparticles: Characteristics and Applications". *Acta Scientific Pharmaceutical Sciences* 8.6 (2024): 07-18.

## Introduction

Various nanomaterials with antimicrobial properties have been used in biocides for over 120 years (Bernd Nowack). However, nanoparticles received more recognition only in the second half of the 20th century. Until 19th century, antimicrobial and physicochemical properties could not be accurately assessed due to the lack of technologies (XiuYi Yang). Today, antibiotics are considered as the "gold standard" in treatment of many bacterial infections [Julian Davies, F. Cavalieri]. However, microorganisms can develop antibiotic resistance as a result of inappropriate use of antibiotics.

The use of nanoparticles based on metals and their oxides in healthcare to combat antibiotic resistance has become a topic of great interest in recent times. One of the well-studied metals affecting biological objects is zinc (Zn) and its oxide (ZnO). Zinc is found in all tissues of the human body, where the highest concentration is found in myocytes (85% of the total zinc content in the body) [1]. Zinc oxide nanomaterials have attracted a lot of attention in this decade because of their enormous potential in a wide range of biomedical applications. Different characterization techniques, such as X-ray powder diffraction, UV–Vis spectroscopy, FTIR, transmission, and scanning electron microscopy, are used for analysis. Zinc oxide nanoparticles (ZnO NPs) have gained immense popularity in various sectors of the healthcare industry and research institutions due to their unmatched physical and chemical characteristics [2]. ZnO has also received a lot of attention in the field of material science due to its indigenous physical as well as chemical characteristics such as excellent chemical stability, high electrochemical coupling coefficient, exceptional photostability, and broad range absorption spectra which has turned it into a multifunctional material [3].It was found that triangular ZnO nanoparticles showed superior antibacterial potential compared to spherical counterparts against the same bacterial strains suggesting that not only the reaction conditions are important but the shapes of prepared nanoparticles can also impact its properties [4].Moreover, smaller size nanoparticles offer enhanced surface area, reactivity, and quantum effects whereas larger ones exhibit distinct optical and electronic features [5,6]. ZnONPs can also operate as an n-type semiconductor, characterized by a band gap energy of 3.37 eV [7]. Their antibacterial efficacy has been discovered to be based on site-specific mechanical disruption of the bacterial cell membrane this increasing bactericidal activity [8]. They are also used in animal nutrition since they have good antimicrobial potency against *E. coli* and *S. aureus* [9].

This article provides a comprehensive overview of different methodologies employed for synthesizing zinc oxide nanoparticles (ZnONPs) using various natural sources such as agro water banana (Musa acuminata), leaf extracts including Croton macrostachyus, Camellia sinensis, Clerodendrum infortunatum, Chenopodium album, Mimosa pudica, as well as mediated synthesis using substances like honey and Eucalyptus robusta Sm. Additionally, it explores the impact of ZnONPs on bacterial cells, particularly in terms of damaging membrane integrity, and examines the effects of incorporating ZnO on surfaces such as PES membranes and its combination with CH drugs. The properties of ZnONPs, including their ability to inhibit bacterial DNA replication pathways, mitigate oxidative stress, and exhibit synergistic effects when combined with other materials, are thoroughly discussed. Furthermore, the article delves into the potential therapeutic applications of ZnONPs in treating various diseases such as fungal keratitis, periodontitis in patients with obstructive sleep apnea (OSA), postpartum endometritis in dairy cattle, and root rot caused by pathogens like A. fumigatus, Candida albicans, multidrug-resistant bacterial strains, and Fusarium oxysporum. It also highlights the inhibitory effects of ZnONPs against a wide range of pathogens including Campylobacter jejuni, methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant strains of *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

### Green synthesis of ZnO nanoparticles

Among nanomaterials, zinc oxide (ZnO) nanoparticles have emerged as promising candidates due to their unique properties, including high surface area, biocompatibility, photocatalytic activity, and antimicrobial efficacy. These properties make ZnO nanoparticles suitable for a wide range of applications, including photocatalysis, sensing, drug delivery, and solar cells.

Traditional methods for synthesizing ZnO nanoparticles often involve the use of hazardous chemicals, high temperatures, and energy-intensive processes, leading to environmental pollution and health hazards. In contrast, green synthesis approaches offer sustainable alternatives by utilizing natural sources or environmentally friendly agents as reducing and stabilizing agents. These methods not only mitigate environmental impact but also offer cost-effective and scalable routes for nanoparticle production.

The green synthesis of ZnO nanoparticles typically involves the utilization of plant extracts, microbial cultures, algae, or other bioresources rich in bioactive compounds such as polyphenols, flavonoids, and terpenoids. These compounds act as reducing agents, facilitating the reduction of zinc ions and the formation of ZnO nanoparticles under mild reaction conditions. Additionally, green synthesis methods often employ water as a solvent, further minimizing environmental footprint compared to organic solvents used in conventional synthesis routes.

A study at Adama Science and Technology University used plant extract to synthesize nanoparticles Ag2O/CuO/ZnO nano composites using aqueous extract of Croton macrostachyus leaf for Photo degradation, and ternary nanocomposites demonstrating efficient degradation of organic contaminants in wastewater and strong antioxidant properties. The nanocomposites, containing secondary metabolites, efficiently degraded methylene blue dye and scavenged DDPH free radicals [10].

In Honey mediated synthesis of ZnONPS via a greener approach using honey as a bio reductant and stabilizing agent, the antimicrobial activity of ZnONPs was performed against clinical strains of Gram negative bacteria such as Klebsiella pneumoniae (K. pneumoniae), Escherichia coli (E. coli), and Gram positive bacteria Methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa (P. aeruginosa), and Staphylococcus aureus (S. aureus) was assessed along with their antibiofilm activity. The evaluation of the integrity of the bacterial cell membrane with the leakge of cellular components, including nucleic acids and proteins, into the culture medium indicated that honey synthesized ZnONPs could function as potential antimicrobial agents.Other experiments include synthesizing ZnO using LBG as a complexing agent [11].A study by droepenu., *et al*., examined the effect of two morphological nanostructures of Eucalyptus robusta Sm mediated ZnONPs based on their different calcination temperatures and their antimicrobial and antifungal potential on some selected pathogens using disc diffusion method [12].

Magnesium, copper and zinc oxide nanoparticles have been synthesized from Camellia sinensis (tea) leaf extract in an environmentally friendly way. The prepared metal oxide nanoparticles were tested for their fungicidal activity against the fungi *pestalotiopsis theae*, which causes grey blight disease, and pesticide activity against the pest *oligonychus coffeae*, which causes red spider mites disease in plants, particularly in tea plants [13].

Synthesize Zinc Oxide Nanoparticles (ZnO NPs) using agro-waste banana (Musa acuminata) leaves has been explored by shivitraloshini., *et al*. in which both the biogenic and chemogenic ZnO NP has been compared. The biogenic ZnO NP exhibited a larger surface area which enhanced an inhibitory effect to kill foodborne bacteria (S. typhimurium, and S. aureus). Moreover, the biogenic films showed enhanced physicochemical properties as compared to chemogenic films and pristine chitosan. The successful biogenic ZnO NP has superior properties to chemogenic ZnO NP.[14]. The antimicrobial effectiveness against Staphylococcus aureus and Salmonella typhimurium was examined via the Disk Diffusion method. Bio-nanocomposites were developed by integrating varying concentrations of ZnO nanoparticles (ZnONPs) into chitosan using the solvent casting technique. The antibacterial performance of these bio-nanocomposites was evaluated against both bacterial strains using the Viable Cell Colony Count method. This green synthesis approach, employing Clerodendrum infortunatum leaf aqueous extract for the production of zinc oxide nanoparticles (CIAQ-ZnONPs), holds promise for a range of therapeutic and biomedical [15].

Another study reports extracellular mycosynthesis of two nano metal oxides mediated by *Aspergillus sojae* mycelial cell-free filtrate (MCFF). *A. sojae* MCFF was reacted with cobalt chloride hexahydrate and zinc nitrate hexahydrate for the preparation of Co3O4 NPs and ZnO NPs, respectively. *A. sojae*-derived Co3O4 NPs and ZnO NPs can be potential candidates for use as antimicrobial nano metal oxides in food and pharmaceutical industries [16].

Green synthesis of ZnONPs using *Mimosa pudica* leaf extract as a reducing, stabilizing, and capping agent that can act as an alternative therapeutics. Furthermore, the antibacterial and antibiofilm activity of MP-ZnONPs was assessed against multidrug-resistant (MDR) uropathogens, including both Gram-negative *Escherichia coli* (*E. coli*) and Gram-positive *Staphylococcus aureus* (*S. aureus*) strains9.the green synthesis of ZnO nano-crystals [17]. An aqueous extract of C*henopodium album* leaf was used as a biological reducing agent for the fabrication of ZnO nano-crystals from the zinc sulphate heptahydrate. Compared to Gram-positive bacteria, ZnO nano-crystals showed more resistance to Gram-negative bacteria. This green synthesis route of ZnO nano-crystals is novel and aims to reduce the use of toxic chemicals in fabricating the nanoparticles of functional oxides, which have a wide range of potential applications in general and biomedical science [18].

| Source | Antimicrobial resistance against | Application | Reference |
|---|---|---|---|
| Honey | Clinical strains of Gram-negative bacteria such as *Klebsiella pneumoniae (K. pneumoniae), Escherichia coli (E. coli),* and Gram positive bacteria Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa (P. aeruginosa*), and *Staphylococcus aureus (S. aureus)* was assessed along with their antibiofilm activity. | biomedical and pharmaceutical fields. | [11] |
| *Eucalyptus robusta Smith* aqueous leaf extract | ZnO NS400 sample showed an enhanced activity against *S. aureus* (17.2 ± 0.1 mm) bacterial strain and *C. albicans* (15.7 ± 0.1 mm) fungal strain at 50 mg/ml. | Medicine, agriculture, and aquaculture industry in combating some of the pathogens | [12] |
| *Camellia sinensis* (tea) leaf extract(Elangovan Jayaseelan a) | They were tested as pesticides and fungicides against *Oligonychus coffeae* (red spider mites) and *Pestalotiopsis theae* (grey blight disease).ZnO nanoparticles showed better activity compared to the CuO and MgO nanoparticles for pesticidal activity. | This kind of mesoporous material modified nanoparticles prepared by green methods can result in enhanced activity of potential fungicidal and pesticidal nanoparticles for large scale applications in the future. | [13] |
| Croton macrostachyus leaf | Ag2O/CuO/ZnO nanocomposites and their metal oxide nanoparticles exhibited potent antioxidant activity against DDPH radicals. | Nil | [10] |
| Musa acuminata | Biogenic ZnO NP had greater inhibitory action against both Staphylococcus aureus and Salmonella typhimurium than chemogenic ZnO NP. | Resulting biofilms exhibit the potential to enhance food quality, safety, and longevity in the food industry. | [14] |
| *Clerodendrum infortunatum* | Synthesized nanoparticles demonstrated antibacterial efficacy against gram-positive and gram-negative bacterial pathogens. | Therapeutic and biomedical applications. | [15] |
| *Aspergillus sojae* | Metal oxide NPs exhibited significant *in vitro* antibacterial potency against *E. coli, S.* Typhimurium, and *S. aureus*. | *A.sojae*-derived Co3O4 NPs and ZnO NPs can be potential candidates for use as antimicrobial nano metal oxides in food and pharmaceutical industries. | [16] |
| Mimosa pudica leaf extract | It was assessed against multidrug-resistant (MDR) uropathogens, including both Gram-negative *Escherichia coli* (*E. coli*) and Gram-positive *Staphylococcus aureus* (*S. aureus*) strains.It showed an anticancer efficiency for cancerous MCF7 cells in comparison with the standard RAW 264.7 cells. | Biogenic Mp-ZnONPs hold great promise for biomedical and environmental applications, along with urinary tract infections due to their eco-friendly synthesis, antibacterial efficacy, non-toxic nature, and biocompatibility. | [17] |
| Chenopodium album | Experiment was done where ZnO nano-crystals showed more resistance to Gram-negative bacteria than Gram-positive bacteria. | They have a wide range of potential applications in general and biomedical science, in particular | Sadiya Samar a 1) |

**Table 1:** Sources of ZnO Nps Synthesis.

## Effects of ZnO nanoparticles

Because of its ability to absorb UV radiation and possess catalytic, antibacterial, and semiconducting properties, zinc oxide nanoparticles (ZnO NPs) are increasingly being used in consumer goods. A study by Atapakala., *et al*. found that the release of cellular constituents like nucleic acids and proteins in the culture medium revealed damaged bacterial cell membranes. The absorbance of the supernatant collected after ZnO nanoparticles treatment increased significantly, indicating the release of cellular constituents into the cell suspension. This damage, caused by reactive oxygen species, allowed the cell's DNA/RNA or proteins/amino acids to migrate into the media. The study confirmed that ZnONPs exhibited potential antibacterial activity through membrane integrity damage against pathogenic *E. coli* and *K. pneumoniae* bacteria. Morphological studies revealed irregularly wrinkled outer surfaces, fragmentation, and aggregation of injured cells or cellular debris when exposed to ZnONPs at their respective MBC concentrations for 16 hours. ZnONPs have been found to have antibacterial properties due to their ability to transport zinc ions into cells. The outer layer of Gram-ve bacteria cells, which has a thin coating of peptidoglycan and porins, allows ZnONPs to enter cells passively. These chelated zinc ions can inhibit enzymes like alkaline phosphatases, polymerases, and carboxypeptidases. Smaller ZnONPs can break through bacterial membranes, enhancing their antimicrobial properties. Green-synthesised ZnONPs are bactericidal, targeting the respiratory chain and cell division, ultimately leading to cell death [11]. A ZnO/PHMB membrane fabricated by mengna., *et al*., provides with excellent antimicrobial and antifouling capabilities was developed by coating synthesized nanocomposites onto a PES membrane surface. The nanocomposites showed a 99.99% bactericidal rate with minimal PHMB addition, reducing the required dosage of bactericide PHMB in antimicrobial applications. All ZnO/PHMB membranes exhibited a substantial reduction in bacterial cell viability compared to either PDA or PES membranes. Particularly, 200ZP, 400ZP, 600ZP, and 800ZP membranes exhibited inactivation rates of about 79.58%, 88.92%, 92.80%, and 95.23%, respectively. This can be further demonstrated with the remarkably suppressed colony formations of ZnO/PHMB membranes [19].

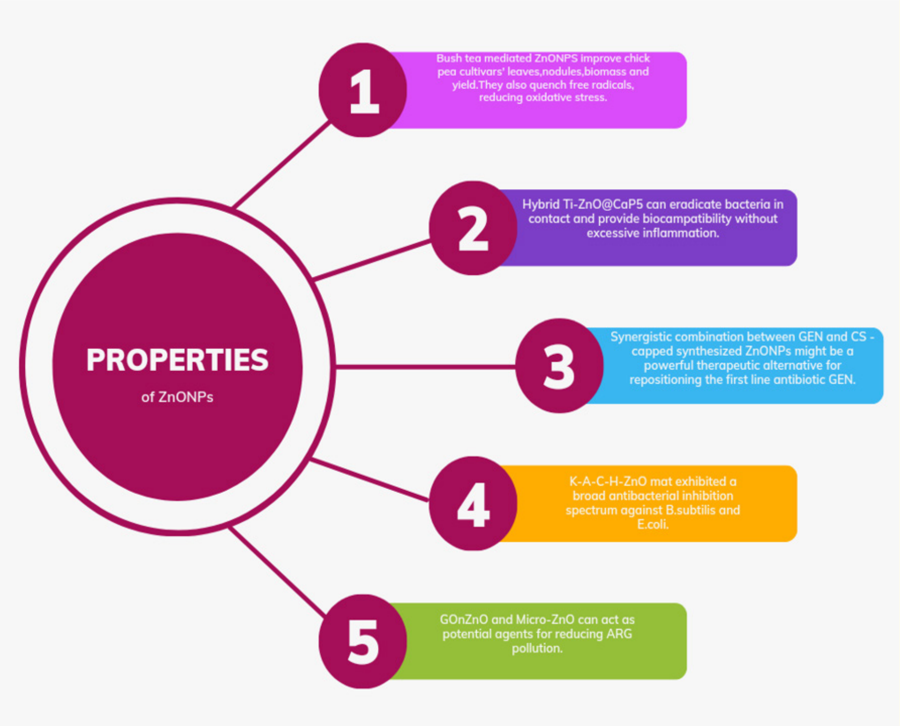
A study by Titiradsadakorn Jaithon where mangosteen peel ethanol extract was utulized to find the accumulation of chlorophylls and carotenoids. The results showed that ZnO-Gm-E application (at 1.90 and 3.80 mg/mL) significantly ($p < 0.05$) increased the content of chlorophyll a, which is the major photosynthetic pigment. A similar result was found in olive trees. The observed effects could be attributed to the potential influence of ZnO NPs on stimulating the gene expression of enzymes involved in chlorophyll biosynthesis [20].

The combination of CH drug and ZnO NPs increases antibacterial efficacy against Bacillus Subtilis and Escherichia coli. the concentration of the green synthesized ZnO nanoparticles (ZnO NPs) using C. roseus (leaf extract) and M. recutita (Chamomile flower part) herbal drug (CH)) can easily interact with bacterial surface and enters into the cell and exhibit superior bactericidal effects. Administration of GOnZnO treatment led to a significant increase in the expression of antibiotics Ctra_murA_FOF and APH (3′)-IIIa, while the Micro-ZnO group exhibited enhanced MLS (macB and vatB) expression. Herein, the expression levels of various DNA replication genes, including DNA polymerase III holoenzyme, dnaB, dnaG, RNeseH, polA, and Lig, were significantly lower in the GOnZnO group than in the nZnO group (Fig. 3A). Furthermore, compared to the GOnZnO group, the Micro-ZnO group exhibited even lower expression levels of these genes (Fig. 3A). These results indicate that both GOnZnO and Micro-ZnO can inhibit bacterial DNA replication pathways, with Micro-ZnO exerting a stronger inhibitory effect [21]. Biosynthesized ZnO NPs, capped with C. sinensis leaf extract, showed enhanced antibacterial activity compared to plant extracts. The capping action of the leaf extract reduced particle size, enhancing antibacterial activity. The inhibition zone of PVA aerogel microsphere increased with loaded ZnO NPs against MDR bacteria. Coating ZnO NPs with modifying agents like biopolymers also enhanced their antibacterial activity [22]. ZnO-based thin films have been obtained using pulsed laser deposition (PLD) techniques, The antibacterial effect of ZnO is well known, through the production of reactive oxygen species (ROS) and oxygenated water that act chemically on the integrity of the bacterial cell wall. Doping with Sn leads to the formation of voids in the film and facilitates the release of Zn ions, resulting in increased antimicrobial activity These thin films have promising properties for medical applications, such as coating implantable materials with metals, alloys, or bioinert ceramics to support healing and reduce bacterial infection at the surgery site [23].

Biogenic nanoparticles (MNPs) have shown potent antibacterial properties due to their interaction with negatively charged cell walls of bacteria, increasing membrane permeability and disrupting cell integrity. They can induce oxidative stress by generating reactive oxygen species (ROS) within bacterial cells, deactivating antioxidant defenses. This non-specific mechanism makes MNPs difficult for bacteria to develop resistance mechanisms and expand their antibacterial spectrum. In a study, the MIC values for ATCC 25922, PG2, and CSA1 were 200 µg/ml, 25 µg/ml, 400 µg/ml, and 400 µg/ml, respectively. The agar well diffusion method showed clear zones at higher concentrations, possibly due to the negative surface charge of Mp-ZnONPs [17].

## Properties of Zno Nanoparticles

ZnO NPs are one of the most widely used metal oxide NPs in a variety of sectors and research institutions since they possess significant applications. Because of the small particle size of nano-ZnO, the human body can easily absorb zinc. Since ZnO NPs are relatively affordable and less toxic than other metal oxide NPs, they offer a wide range of other medicinal uses, including antimicrobial, anti-diabetic, anti-inflammatory, anti-aging and also in wound healing and bio-imaging. It is researched and evaluated that bush tea-mediated ZnO NPs improve chickpea cultivars' leaves, nodules, biomass, and yield under glasshouse conditions. The nanoparticles also exhibit inhibitory activities against bacteria, particularly E. coli and S. aureus. They also quench free radicals, reducing oxidative stress and potentially fighting diseases against humans and plants.[24]. In vivo studies show that hybrid Ti-ZnO@CaP5 can eradicate bacteria in contact and provide biocompatibility without excessive inflammation. This study provides insights into designing multifunctional biomaterials for bone implants, paving the way for better clinical outcomes as bone implant design faces challenges in balancing antibacterial and pro-osteogenic abilities. Zinc oxide (ZnO) nanorods grown hydrothermally on Ti-based implants can improve antibacterial properties but cannot meet implant requirements due to rapid degradation and uncontrolled leaching. A lattice-damage-free method is adopted to modify ZnO nanorods with thin calcium phosphate (CaP) shells. This prevents rapid degradation and ensures sustained release of $Zn^{2+}$ ions. The nanorods induce osteogenic performance and exhibit excellent antibacterial ability against S. aureus and E. coli bacteria.[25]. The bactericidal synergistic combination between gentamycin and CS-capped synthesized ZnO NPs might be a powerful therapeutic alternative for repositioning the first-line antibiotic GEN as a study investigates the synergistic effects of zinc oxide nanoparticles (ZnO NPs) in combination with Gentamicin (GEN) against various bacterial strains. Results show ZnO NPs with MICs ranging from 0.002 to 1.5 µg/mL, while precursor salts displayed MICs of 48.75–1560 µg/mL. Chitosan (CS)-capped ZnO NPs exhibited even lower MICs than uncapped counterparts. Combinations of CS-capped synthesized ZnO NPs and GEN proved highly effective, inhibiting bacterial growth at significantly lower concentrations than GEN or ZnO NPs alone. This is due to the conformational coating of CS on the ZnO NPs' surface, which enhances the positive particle surface charge. [26]. ZnO nanoparticles have been found to have long-term antibacterial effects, promoting wound healing, tissue regeneration, and neovascularization. The concentration of these nanoparticles can easily interact with bacterial surfaces, exhibiting superior bactericidal effects. The K-A-CH-ZnO mat showed a remarkable bacterial effect against Bacillus Subtilis than Escherichia coli due to its thin peptidoglycan layer and strong electrostatic interaction. The drug release curve showed that 21% and 28% of ZnO were released in 24 hours and 50% and 57% in 144 hours. The K-A-CH-ZnO mat also exhibited a broad antibacterial inhibition spectrum against B. subtilis (8.9 mm) and E. coli (7.5 mm) [27]. Antibiotic Resistance Genes (ARGs) are present in various environments, including animal agriculture and waste products. Metagenomic sequencing showed that Graphene Oxide-modified Zinc Oxide (GOnZnO) and Microorganism-mediated Zinc Oxide (Micro-ZnO) significantly reduced zinc levels in animal manure. The expression levels of DNA replication genes were lower in GOnZnO and Micro-ZnO groups, while GOnZnO and Micro-ZnO had no significant impact on archaeal DNA replication pathway-related genes. These findings suggest GOnZnO and Micro-ZnO as potential agents for reducing ARG pollution [21]. Zinc oxide nanoparticles were synthesized using precipitation methods and surface modified with PEG. The resulting crystalline and hexagonal ZnONP showed enhanced antimicrobial activity against S. aureus and E.coli bacteria. The enhanced generation of reactive oxygen species (ROS) at the bacterial interface was found to be crucial for this higher antimicrobial activity [28].The Cs/Ge blend loaded with Co-doped ZnO NPs nanocomposites have excellent optical, dielectric, and electrical properties as the interaction between Cs/Ge and Co-doped ZnO NPs reveals changes in crystallinity and amorphousness. making them ideal for energy storage systems and antibacterial activity against bacteria [29].



1. Bush tea mediated ZnONPS improve chick pea cultivars' leaves,nodules,biomass and yield.They also quench free radicals, reducing oxidative stress.
2. Hybrid Ti-ZnO@CaP5 can eradicate bacteria in contact and provide biocampatibility without excessive inflammation.
3. Synergistic combination between GEN and CS - capped synthesized ZnONPs might be a powerful therapeutic alternative for repositioning the first line antibiotic GEN.
4. K-A-C-H-ZnO mat exhibited a broad antibacterial inhibition spectrum against B.subtilis and E.coli.
5. GOnZnO and Micro-ZnO can act as potential agents for reducing ARG pollution.

**Figure b**

## Therapeutic applications of ZnO Nps

ZnO NPs have a high biocompatibility, allowing it to be used in a therapeutic environment for antibacterial, antifungal, antiviral, and anticancer properties Several types of inorganic metal oxides, such as TiO2, CuO, and ZnO have been produced and have remained in current investigations, but ZnO NPs are the most interesting of these metal oxides since they are inexpensive to make, safe, and simple to prepare. Meso-ZnO, a carrier for NATA, enhances drug release and bioavailability, inhibiting A. fumigatus growth and fungal biofilm formation. It also protects against fungal keratitis by activating autophagy, reducing inflammation and improving prognosis, suggesting Meso-ZnO/NATA as a potential therapeutic strategy [30].

A serious gum infection that damages gums and can destroy the jawbone is Periodontitis which is linked to obstructive sleep apnea (OSA), with severe OSA more prevalent in stage III periodontitis. The oral microbiome changes due to increased periodontal pathogenic bacteria and Candida albicans. Nanofiber drug delivery systems can be used for local antimicrobial therapy against these microorganisms. A study produced PCL/PLGA nanofibers containing antifungal Amphotericin B, antimicrobial peptide LfcinB Pal, and zinc oxide for inhibiting in vitro polymicrobial biofilms. The nanofibers significantly inhibited nine bacteria viability, Candida albicans viability, and biofilm formation, suggesting a promising strategy for treating periodontitis in OSA patients [31].

*Staphylococcus aureus* (S. aureus) is a major pathogen that causes foodborne diseases in fresh meat products and ready-to-eat (RTE) sandwiches. A study involving zinc oxide nanoparticles (ZnO-NPs) was conducted to combat MDR S. aureus in RTE meat sandwiches. The incidence of S. aureus was found to be high in beef burgers, koftas, sausages, and hot dogs. The ZnO-NPs showed significant antibacterial efficacy against the examined MDR S. aureus isolates, with MIC values ranging from 12.5 to 25 μg/mL. The study suggests that ZnO-NPs could be developed as an effective antibacterial agent to control S. aureus growth in RTE foodThe synthesized ZnO-NPs were characterized via several techniques namely UV–Vis spectroscopy, TEM, XRD, EDX, TGA, FTIR spectroscopy, and Raman spectroscopy. Antibiotic resistance genes (*aac*A-*aph*D, *aad*E, *apm*A, *bla*Z, *cfr*, *mec*A, *spc*, and *van*A) and virulence genes (*clf*A, *fnb*A, *fnb*B, *pvl*, *tst*) and SEs (*sea*, *seb*, *sec*, *sed*, and *see*) were analyzed for their prevalence. The antibacterial efficacy of ZnO-NPs was examined at various concentrations, revealing remarkable effectiveness against MDR *S. aureus* [32].Another study demonstrates the green synthesis of silver/zinc oxide nanocomposites (Ag/ZnO NCs) using Curcuma longa stem and leaves, showing promising antibacterial activity against multi-drug-resistant pathogens. UV-Vis spectroscopy, Fourier transform infrared spectroscopy, thermogravimetric analysis, and powder X-ray diffraction confirmed the synthesis. This suggests further exploration as a potential antibiotic alternative [33]. Recent research has led to the development of zinc oxide nanoparticles (ZnO NPs) for treating Postpartum endometritis caused by MDR bacterial strains in dairy cattle. ZnO significantly decreased pathogenic bacteria, including E. coli and S. aureus, and achieved a high cure rate. This study highlights the potential of ZnO as a substitute antimicrobial agent for treating uterine illness as treatment is challenging due to high antibiotic failure risk.

In conclusion, ZnO NPs have a wide range of antibacterial and anticancer actions due to the higher capability to generate ROS against microorganisms that cause bovine endometritis. ZnO NPs are suggested to protect uterine microflora by reducing pathogenic bacteria, including *E. coli*, *S. aureus* and mixed infections between them [34]. Few studies evaluates the effectiveness of single or combinational use of cinnamon oil, encapsulated curcumin, and zinc oxide nanoparticles against the foodborne pathogen Campylobacter jejuni using RNA-seq. The single-agent treatment showed significant antimicrobial effects like altered gene expression while the combination showed synergistic effects. The study provides insights into combating Campylobacter while minimizing the development of antimicrobial resistance in long-term usage. The combination of cinnamon oil and curcumin provoked cellular signaling but repressed chemotaxis-associated genes. This research offers new insights into combating antibiotic resistance in animal farms or serving as alternative antimicrobials during food processing [35]. Locust Bean Gum (LBG) was used as a biotemplate for synthesizing ZnO nanoparticles for the first time. The NPs showed excellent photocatalytic activity, antimicrobial activity (against B subtilis), and significant cell death in breast, ovarian, and lung cancer cell lines. They also blocked cell migration in wound healing assays. Further optimization of nanostructure properties could make LBG a promising candidate for nano-biotechnology and bioengineering due to its wide range of potential applications [36].

Study by alice., *et al*., synthesized and characterized zinc oxide nanoparticles (ZnONPs) using laser-ablation at 100 mJ. The spherical ZnONPs showed antimicrobial activity against ophthalmological bacteria, MRSA, and Pseudomonas aeruginosa. They also showed moderate antioxidant and free radical scavenging activity. ZnONPs prepared with 20 min ablation time were safer and more biocompatible than those with 30 min ablation time. This suggests ZnONPs could have laser-activated antimicrobial activity for ophthalmological applications and treating retinal disorders, but further functional tests are needed [23].

Camellia sinensis leaf extract shows promising results using metal oxide nanoparticles as seen in the beginning. CuO nanoparticles showed better fungicidal activity, while ZnO nanoparticles showed better pesticidal activity. The modified nanoparticles could be used in various applications, including coating plant parts, removing pests, and spraying. The greener preparation method, easy modification, recycling potential, and small amounts of fungicide and pesticide make these materials attractive for future use. The development of mesoporous material modified nanoparticles could lead to enhanced fungicidal and pesticidal nanoparticles for large-scale applications [13]. A novel ZnO NPs/PVA aerogel microsphere was developed by Fahmi., *et al*., combining PVA with ZnO NPs using a sol-gel method and freeze-dried cycle. The NPs were biosynthesized using C. sinensis leaf extract and analyzed using various techniques. The composite showed significant antibacterial activity against MDR bacteria, including K. pneumoniae, P. aeruginosa, and E. coli. The biocompatible and highly bactericidal properties of the composite have potential for therapeutic applications [22]. Aishah., *et al*., produced linalool loaded zinc oxide nanocomposite (LZNPs) and evaluated their antileishmanial effects against Leishmania major. LZNPs showed significant antileishmanial effects on promastigotes and amastigotes, increasing apoptotic cells and upregulating gene expression. LZNPs reduced the diameter and parasite load of Leishmania major lesions in mice, and increased antioxidant enzyme expression through its antioxidant and immunomodulatory properties. Further investigation could explore the potential use of LZNPs in managing and treating Leishmania major [37]. ZnO-S. cerevisiae, a new compound, has been synthesized to combat root rot, a common disease which is caused by *Fusarium oxysporum* in Astragalus memeranaceus. It inhibits pathogens by down-regulating physiological genes, reducing disease severity

| Synthesis | Uses | reference |
|---|---|---|
| Meso-ZnO | Used for inhibiting A. fumigatus growth | Lingwen Gu., *et al*., |
| A study produced PCL/PLGA nanofibers containing antifungal Amphotericin B, antimicrobial peptide LfcinB (21-25) Pal, and zinc oxide for inhibiting in vitro polymicrobial biofilms | It inhibited bacteria viability, Candida albicans viability, and biofilm formation | Mayra A. Téllez Corral., *et al*., |
| ZnO-NPs | Inhibits MDR S. aureus | (Mabrouk Sobhy a b,) |
| (Ag/ZnO NCs) using Curcuma longa stem and leaves. | Multi-drug resistant (MDR) pathogens | Pokkittath Radhakrishnan Arya a) |
| Biologically synthesized ZnO NPs from a green natural source of Helianthus annuus seeds**.** | MDR bacterial strains in dairy cattle**.** | Yahia A. Amin **a** |
| Combinational use of three antimicrobials, including cinnamon oil, encapsulated curcumin and zinc oxide nanoparticles (ZnO NPs), | Used against a leading foodborne pathogen Campylobacter jejuni**.** | Mohammed J. Hakeem a **b** |
| ZnO nanoparticles synthesized using Locust Bean Gum (LBG)as a biotemplate | Exhibited antimicrobial activity in both *Staphylococcus aureus* and *Bacillus subtili***s** | Amol Kahandal **a** |
| ZnONPs using laser-ablation at 100 mJ with different ablation times. | It showed antimicrobial activity against ophthalmological bacteria, MRSA, and Pseudomonas aeruginosa. | Alice-Maria Olteanu a) |
| ZnONPs synthesized from Camellia sinensis leaf extract. | To treat grey blight disease and red spider mites disease in plants caused by fungi pestalotiopsis theae, and pesticide activity against the pest oligonychus coffeae respectively. | Elangovan Jayaseelan a |
| Linalool loaded zinc oxide nanocomposite (LZNPs). | Their antileishmanial effects against Leishmania major were evaluated. | (Aishah E Albalawi a,) |
| ZnO-S. cerevisiae | To treat a common disease in Astragalus membranaceus caused by *F.oxysporum* | Yaowu Su a b) |
| A novel ZnO NPs/PVA aerogel microsphere was developed by compositing an aqueous solution of PVA with ZnO NPs using a sol-gel method and freeze-dried cycle were biosynthesized using *C. sinensi*s leaf extract. | It exhibited significant antibacterial activity against MDR *K. pneumoniae, P. aeruginosa*, and *E. col*i**.** | May Fahmi Abdulrahman a**)** |

**Table 2:** Therapeutic applications ZnO Nps.

and improving seedling growth. The compound also activates antioxidant enzymes, enhances antifungal metabolites, and induces resistance genes, offering a promising alternative to traditional antifungal agents [38].

## Conclusion

Zinc oxide nanoparticles have significant antibacterial potential. The use of various methods of synthesis, chemical modification, as well as joint use with other nanomaterials affects the physical and morphological characteristics of nanoparticles, which, in turn, leads to a change in their antibacterial properties.The review highlights recent methods of synthesizing ZnONPs using agro water banana (Musa acuminata),Extracts of leaves like *Croton macrostachyus*, *Camellia sinensis, Clerodendrum infortunatum,* Chenopodium album, Mimosa pudica, and other methods of mediated synthesis of ZnONPs using honey, Eucalyptus robusta Sm, A. sojae MCFF. The effects of ZnONPs on bacterial cells like cell membrane integrity damage and DNA replication inhibition due to its various antibacterial properties are given along with its inhibitory activities against bacteria, particularly *E coli*, *B.subtilis*, and *S.aureus*. The recent research where ZnONPs are used as potential therapeutics are also given in brief like it's potential in treating Fungal keratitis, Periodontitis in patients with OSA, Postpartum endometritis in dairy cattle and Root rot by inhibiting A. fumigatus, Candida albicans, MDR bacterial strains and Fusarium oxysporum respectively. This has increased the use of ZnONPS in inhibiting the growth of pathogens especially when used in combination with other materials. Thus the synergistic effects cause an increase in the efficacy of the nanoparticle due to the change in its antimicrobial properties. As a result, nanoparticles based on zinc oxide are increasingly used not only in nanoelectronics and optics, but also in such industrial areas as cosmetic, food, rubber, pharmaceutical, household chemicals, etc. Thus, ZnONPs can be considered as a promising new generation antimicrobial agent.

## Bibliography

1. A Król., *et al*. "Zinc oxide nanoparticles: Synthesis, antiseptic activity and toxicity mechanism". *Advances in Colloid and Interface Science* 249 (2017): 37-52.
2. A Sirelkhatim., *et al*. "Review on zinc oxide nanoparticles: Antibacterial activity and toxicity mechanism". *Nano-Micro Letters* 7 (2015): 219-242.
3. DK Sharma., *et al*. "A review on ZnO: Fundamental properties and applications". *Materials Today: Proceedings* 49 (2020): 3028-3035.
4. BK Sharma., *et al*. "Green Synthesis of Triangular ZnO Nanoparticles Using Azadirachta indica Leaf Extract and Its Shape Dependency for Significant Antimicrobial Activity: Joint Experimental and Theoretical Investigation, Journal of Cluster Science. 33 (2022): 2517-2530.
5. B Gherbi., *et al*. "Effect of pH Value on the Bandgap Energy and Particles Size for Biosynthesis of ZnO Nanoparticles: Efficiency for Photocatalytic Adsorption of Methyl Orange". *Sustainability (Switzerland)* 14 (2022).
6. J Pan., *et al*. "Size Tunable ZnO Nanoparticles to Enhance Electron Injection in Solution Processed QLEDs". *ACS Photonics* 3 (2016): 215-222.
7. PK Mishra., *et al*. "Zinc oxide nanoparticles: a promising nanomaterial for biomedical applications". *Drug Discovery Today* 22 (2017): 1825-1834.
8. N Padmavathy and R Vijayaraghavan. "Enhanced bioactivity of ZnO nanoparticles - An antimicrobial study". *Science and Technology of Advanced Materials* 9 (2008).
9. MSR Barreto., *et al*. "*In vitro* physiological and antibacterial characterization of ZnO nanoparticle composites in simulated porcine gastric and enteric fluids". *BMC Veterinary Research* 13 (2017): 1-10.
10. T Jabessa Masho., *et al*. "Green synthesis, characterization of Ag2O/CuO/ZnO nano composites using aqueous extract of Croton macrostachyus leaf for Photo degradation, anti-microbial and antioxidant activities". *Results in Chemistry* 7 (2024): 101369.
11. S Atapakala., *et al*. "Honey mediated synthesis of zinc oxide nanoparticles, and evaluation of antimicrobial, antibiofilm activities against multidrug resistant clinical bacterial isolates". *Journal of Industrial and Engineering Chemistry* (2024).
12. EK Droepenu., *et al*. "Study of the antimicrobial activity of zinc oxide nanostructures mediated by two morphological structures of leaf extracts of Eucalyptus radiata". *Heliyon* 10 (2024): e25590.
13. E Jayaseelan., *et al*. "Role OF KIT-6 on the fungicide and pesticide activities of zinc, copper and magnesium oxide nanoparticles prepared using Camellia sinensis extract (tea plant): through green synthesis". *Nano-Structures and Nano-Objects* 38 (2024): 101119.
14. S Sasidharan., *et al*. "Tanislaus Antony Dhanapal, Development of novel biofilm using Musa acuminata (waste banana leaves): mediated biogenic zinc oxide nanoparticles reinforced with chitosan blend". *Journal of King Saud University - Science* 36 (2024): 103080.
15. S Kumar., *et al*. "Phyto-mediated synthesis of zinc oxide nanoparticles from Clerodendrum infortunatum L. leaf extract and evaluation of antibacterial potential". *South African Journal of Botany* 164 (2024): 146-151.
16. BA Omran and KH Baek. "Dual extracellular mycofabrication of cobalt and zinc nano metal oxides mediated by mycelial-cell free filtrate of Aspergillus sojae: Characterization and assessment of antibacterial activity". *Journal of Molecular Structure* 1300 (2024): 137190.

17. S Pany., *et al*. “Bio-fabrication of ZnONPs using Mimosa pudica Extract to Combat Multidrug Resistant Uropathogens”. *Journal of Industrial and Engineering Chemistry* (2024).

18. S Samar., *et al*. “Green synthesis of ZnO nano-crystals using *Chenopodium album* L. Leaf extract, their characterizations and antibacterial activities”. *Materials Science and Engineering: B* 299 (2024): 117005.

19. M Li., *et al*. “Development of an antimicrobial and antifouling PES membrane with ZnO/poly(hexamethylene biguanide): nanocomposites incorporation”. *Chemical Engineering Journal* 481 (2024): 148744.

20. T Jaithon., *et al*. “Potential usage of biosynthesized zinc oxide nanoparticles from mangosteen peel ethanol extract to inhibit Xanthomonas oryzae and promote rice growth”. *Heliyon* 10 (2024): e24076.

21. H Zhang., *et al*. “Potential of novel zinc-based nanomaterials on the microbial community, antibiotic resistance genes, and DNA replication in animal manure”. *Chemical Engineering Journal* 481 (2024).

22. MF Abdulrahman., *et al*. “Preparation of polyvinyl alcohol (PVA): aerogel microsphere loaded with biogenic zinc oxide nanoparticles as potential antibacterial drug”. *Journal of Molecular Structure* 1306 (2024): 137901.

23. AM Olteanu., *et al*. “Antibacterial activity of tin-doped zinc oxide thin films deposited by laser ablation”. *Ceramics International* 50 (2024): 3497-3510.

24. AG Kaningini., *et al*. “Evaluation of the antimicrobial activity and chickpea growth stimulation effects of green synthesized zinc oxide nanoparticles”. *Plant Stress* 12 (2024): 100442.

25. I Ullah., *et al*. “Diffusion-driven fabrication of calcium and phosphorous-doped zinc oxide heterostructures on titanium to achieve dual functions of osteogenesis and preventing bacterial infections”. *Acta Biomaterialia* 175 (2024): 382-394.

26. IR Scolari., *et al*. “Synergistic bactericidal combinations between gentamicin and chitosan capped ZnO nanoparticles: A promising strategy for repositioning this first-line antibiotic”. *Heliyon* 10 (2024): 1-14.

27. LK Sellappan and S Manoharan. “Fabrication of bioinspired keratin/sodium alginate based biopolymeric mat loaded with herbal drug and green synthesized zinc oxide nanoparticles as a dual drug antimicrobial wound dressing”. *International Journal of Biological Macromolecules* 259 (2024): 129162.

28. B Sahoo., *et al*. “Polyethylene glycol functionalized zinc oxide nanoparticle with excellent photocatalytic performance and oxidative stress mediated bacterial cell death”. *Optical Materials* 148 (2024): 114891.

29. LS Alqarni., *et al*. “Enhancing the optical, electrical, dielectric properties and antimicrobial activity of chitosan/gelatin incorporated with Co-doped ZnO nanoparticles: Nanocomposites for use in energy storage and food packaging”. *Journal of Molecular Structure* 1297 (2024): 137011.

30. L Gu., *et al*. “Mesoporous zinc oxide-based drug delivery system offers an antifungal and immunoregulatory strategy for treating keratitis”. *Journal of Controlled Release* 368 (2024): 483-497.

31. MA Mariño., *et al*. “Agroindustry Residues as a Source for Cellulose Nanofibers Production”. *Journal of the Brazilian Chemical Society* 32 (2021): 878-888.

32. M Sobhy., *et al*. “Exploring the potential of zinc oxide nanoparticles against pathogenic multi-drug resistance Staphylococcus aureus from ready-to-eat meat and its proposed mechanism”. *Food Control* 156 (2024): 110117.

33. P Radhakrishnan Arya., *et al*. “Facile synthesis of silver-zinc oxide nanocomposites using Curcuma longa extract and its *in vitro* antimicrobial efficacy against multi-drug resistant pathogens of public health importance”. *Inorganic Chemistry Communications* 148 (2023): 110356.

34. YA Amin., *et al*. “Treatment of postpartum endometritis induced by multidrug-resistant bacterial infection in dairy cattle by green synthesized zinc oxide nanoparticles and in vivo evaluation of its broad spectrum antimicrobial activity in cow uteri”. *Research in Veterinary Science* 165 (2023): 105074.

35. MJ Hakeem., *et al*. “Whole transcriptome sequencing analysis of synergistic combinations of plant-based antimicrobials and zinc oxide nanoparticles against Campylobacter jejuni”. *Microbiological Research* 266 (2023): 127246.

36. A Kahandal., *et al*. "Galactomannan polysaccharide as a bio-template for the synthesis of zinc oxide nanoparticles with photocatalytic, antimicrobial and anticancer applications". *International Journal of Biological Macromolecules* 253 (2023): 126787.

37. AE Albalawi., *et al*. "Unveiling of the antileishmanial activities of Linalool loaded zinc oxide nanocomposite through its potent antioxidant and immunomodulatory effects". *Acta Tropica* 252 (2024): 107155.

38. Y Su., *et al*. "ZnO-S.cerevisiae: An effective growth promoter of Astragalus memeranaceus and nano-antifungal agent against Fusarium oxysporum". *Chemical Engineering Journal* 486 (2024): 149958.