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Chitosan-Mediated Green Synthesis of ZnO Nanocomposites Using Medicinal Plants and Sub-Himalayan Ferns: Emerging Perspectives for Antimicrobial, Antibiofilm, Antioxidant and Anticancer Applications

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ABSTRACT

Green synthesis offers an eco-friendly strategy for developing multifunctional nanomaterials with enhanced biocompatibility and biological activity. Chitosan-mediated zinc oxide (ZnO) nanocomposites synthesized using medicinal plants combine the antimicrobial properties of ZnO with the biocompatibility of chitosan and the reducing and stabilizing effects of plant phytochemicals. Medicinal plants and Sub-himalayan pteridophytes provide a rich source of bioactive compounds for the sustainable synthesis of stable ZnO nanocomposites. Chitosan improves nanoparticle stability, controlled Zn^{2+} release, and cellular interactions, thereby enhancing their biological performance. These nanocomposites exhibit potent antimicrobial, antibiofilm, antioxidant, and anticancer activities through mechanisms including membrane disruption, reactive oxygen species generation, biofilm inhibition, and apoptosis induction. This review summarizes recent advances in the green synthesis of chitosan-mediated ZnO nanocomposites, emphasizing synthesis approaches, biological activities, underlying mechanisms, and current challenges related to standardization, biosafety, and clinical translation. These multifunctional nanocomposites hold significant promise as sustainable nanotherapeutics for combating infectious diseases, oxidative stress, and cancer.

***Keywords*:** Chitosan; Zinc oxide nanoparticles; Green synthesis; Medicinal plants; Nanocomposites; Antimicrobial activity; Antibiofilm; Antioxidant; Anticancer.

1. Introduction

Emergence of antimicrobial resistance (AMR), biofilm-associated infection, oxidative stress-related disease and cancer have raised the demand for safer and more effective therapeutic strategies. Among all the nanoparticles, zinc oxide (ZnO) has attracted a lot of interest for its biocompatibility, low toxicity, antimicrobial, antioxidant, wound healing and anticancer properties. The biological activity is mostly attributed to the generation of the reactive oxygen species (ROS), the release of Zn^{2+} ions and interactions with the membranes of the microorganisms and cancer cells. The conventional chemical and physical synthesis, however, requires toxic reagents and high energy input in the process, which restricts the biomedical application. The green synthesis has been recognized as an environmentally benign approach which employs plant extract containing phytochemicals as natural reducing and stabilizing agents to prepare biocompatible ZnO nanoparticles. The medicinal plants and Sub-Himalayan pteridophytes which are still under-explored are abundant source of flavonoids, phenolics, terpenoids and other bioactive compounds which aid in synthesis of nanoparticles and increase their biological activity (Pechnikova et al., 2025). The further functionalization of ZnO nanoparticles by chitosan leads to further improvements in nanoparticle stability, controlled Zn^{2+} release and cellular interactions as well as the introduction of further antimicrobial properties. This is because the synergy between the components (ZnO, chitosan and plant phytochemicals) leads to multifunctional nanocomposites with improved antimicrobial, antibiofilm, antioxidant and anticancer properties. This review provides an overview of the recent progress made in the green synthesis of chitosan mediated ZnO nanocomposites from medicinal plants and Sub Himalayan ferns, along with the techniques used, their biological activities and the major challenges for their biomedical and clinical applications (Maurya et al., 2026).

2. Chitosan-Mediated Green Synthesis of ZnO Nanocomposites Using Medicinal Plants and Sub-Himalayan Ferns

Green synthesis provides an eco-friendly approach for producing ZnO nanoparticles by utilizing plant-derived phytochemicals as natural reducing, stabilizing, and capping agents (Nandhini et al., 2024) (Figure 1). Sub-Himalayan medicinal plants and ferns are rich sources of phenolics, flavonoids, terpenoids, alkaloids, and polysaccharides that regulate nanoparticle formation and enhance biological activity (Banik et al., 2020). While medicinal plants such as *Juniperus indica*, *Ricinus communis*, *Dodonaea viscosa*, *Thymus linearis* have been extensively explored, pteridophytes such as *Woodwardia unigemmata*, *Athyrium filix-femina*, *Diplazium esculentum*, *Pteris vittata*, and *Adiantum capillus-veneris* remain largely underexplored despite their significant phytochemical potential. Chitosan further improves the stability and functionality of ZnO nanoparticles by coordinating with Zn^{2+} ions, preventing aggregation, and promoting controlled Zn^{2+} release (Tundwal et al., 2026).

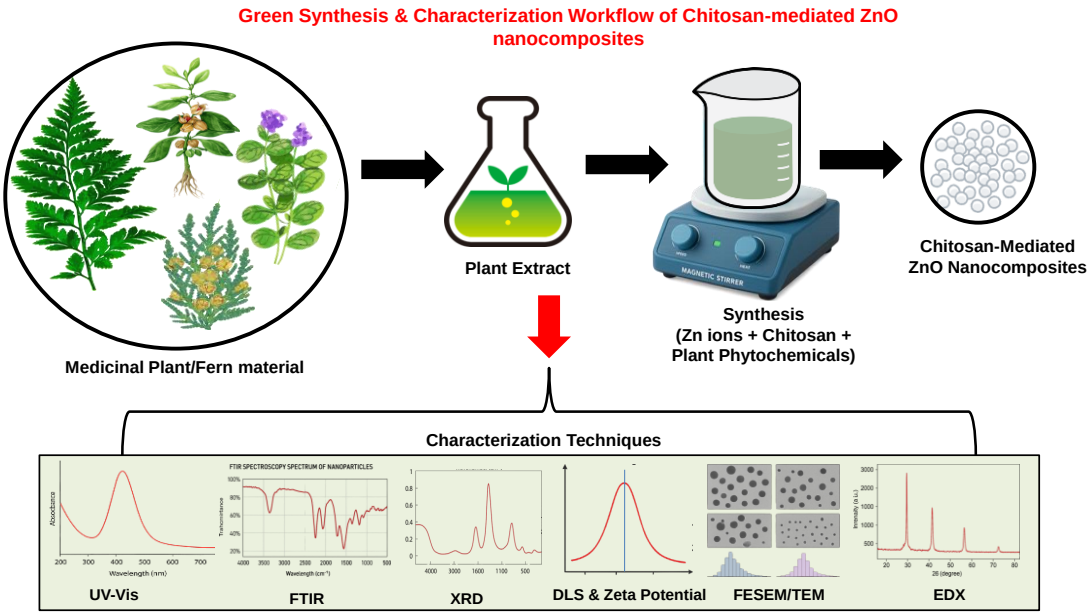

Figure 1: Green Synthesis of Chitosan-Mediated ZnO Nanocomposites from Sub-Himalayan Medicinal Plants and Ferns

During synthesis, plant phytochemicals facilitate the formation of ZnO nanocrystals, while chitosan forms a protective polymeric coating that enhances colloidal stability, dispersibility, and cellular interactions. The physicochemical properties of the resulting nanocomposites, including particle size, morphology, crystallinity, and surface charge, are influenced by synthesis conditions such as pH, precursor concentration, phytochemical composition, and chitosan molecular weight. These characteristics are commonly characterized using UV-Vis spectroscopy, XRD, FTIR, electron microscopy, DLS, zeta potential, and EDX (El-Saadony et al., 2025).The synergistic combination of ZnO, chitosan, and plant phytochemicals generates multifunctional nanocomposites with enhanced antimicrobial, antibiofilm, antioxidant, and anticancer activities, highlighting their potential for sustainable biomedical applications (Srivastava et al., 2025).

3. Biological Activities of Chitosan-Mediated ZnO Nanocomposites Synthesized from Medicinal Plants and Sub-Himalayan Ferns

3.1 Antimicrobial Activity and Underlying Molecular Mechanisms

Multidrug-resistant (MDR) pathogens have appeared fast, emphasizing the need for multifunctional nanomaterials with wide-spectrum antimicrobial properties. The ZnO nanocomposites prepared with the medicinal plants have shown enhanced antimicrobial activity due to the synergistic effect between the added plant phytochemicals and chitosan and ZnO

nanoparticles. They mainly achieve their antimicrobial activity by disrupting the cell membranes, the production of reactive oxygen species (ROS), release of Zn^{2+} ions, and phytochemical-mediated antimicrobial activity (Ahmed et al., 2025) (Figure 2).

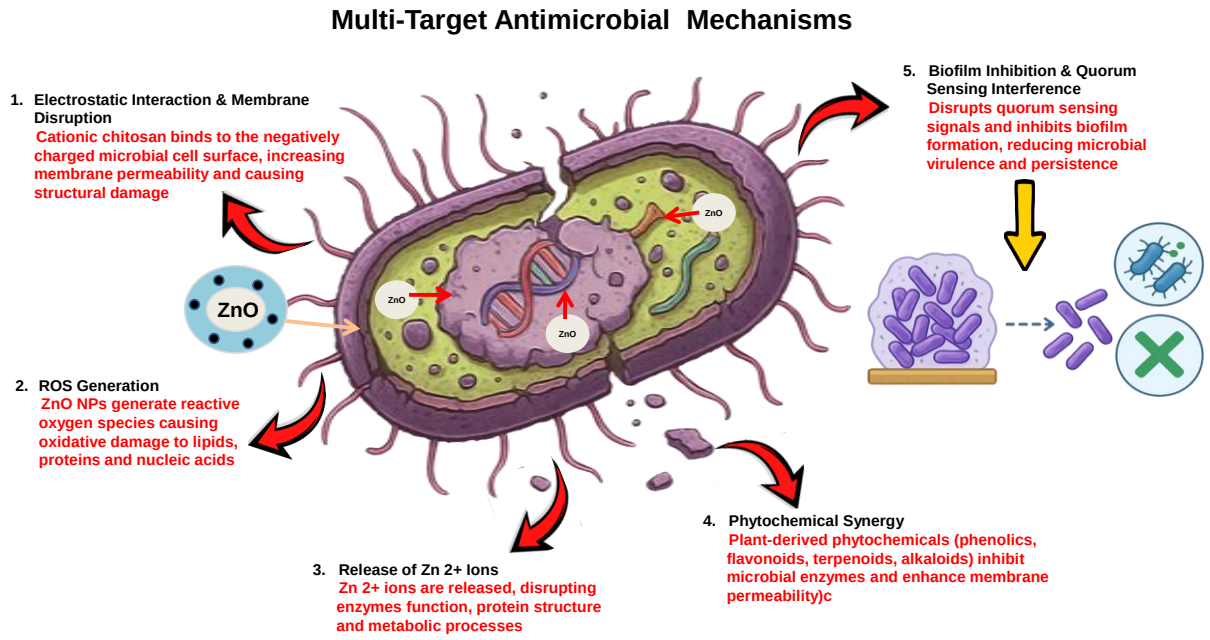

Figure 2: Antimicrobial activity of Chitosan-Mediated ZnO nanocomposites from sub-himalayan medicinal plants and ferns

The chitosan has a positive charge at its amino groups, leading to an increase in the permeability of microbial cell membranes and nanoparticle uptake. ZnO nanoparticles then produce ROS which leads to oxidative damage of membrane lipids, proteins and nucleic acids, and released Zn^{2+} ions cause disruption of the enzymatic activity and metabolism of the cells. Furthermore, antimicrobial activity is further promoted with the presence of plant-derived phytochemicals such as phenolics, flavonoids, terpenoids, and alkaloids, which are able to inhibit microbial enzymes and increase permeability of microbial membranes.

The nanocomposites demonstrate wide-range antimicrobial activity against Gram-positive and Gram-negative bacteria (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) and fungal pathogens (*Candida albicans*). They are also known to inhibit quorum sensing and biofilm formation, and therefore diminish the virulence of microbes and the development of antimicrobial resistance. Chitosan mediated ZnO nanocomposites with their multi target mode of action are promising candidates for next generation antimicrobial therapies (Konkal et al., 2026).

3.2 Antibiofilm Activity: Disruption of Microbial Community Architecture

The treatment of biofilm-associated infections is challenging due to the extracellular polymeric substance (EPS) matrix which provides protection from antimicrobial penetration and increases microbial persistence. The ZnO nanocomposites, prepared by chitosan, effectively prevent the formation of bacterial biofilm by disrupting the adhesion, EPS synthesis, quorum sensing, and maturation of biofilm. The cationic amino groups of chitosan bind with the negative components of biofilm and facilitate penetration of the nanoparticles and destabilize the EPS matrix. This causes the ZnO nanoparticles to produce reactive oxygen species (ROS) and release of Zn^{2+} ions leading to oxidative damage, disruption of membrane function and inhibition of metabolism in bacteria. Furthermore, Zn^{2+} disrupts quorum sensing systems, which lowers the communication and virulence of bacteria and the development of bacterial biofilms. The antibiofilm activity of the phytochemicals is also supported by various other mechanisms that include inhibition of bacterial adhesion and inhibition of the production of exopolysaccharide. Biofilm penetration, controlled release of Zn^{2+} and better anti-biofilm effects are obtained by functionalization of bare ZnO nanoparticles with chitosan. Their properties suggest that they could be good candidates for antimicrobial coatings of wound dressings, implants, catheters, and other biomedical devices to combat chronic biofilm associated infections (Afsharikhah et al., 2025).

3.3 Antioxidant Activity: Regulation of Cellular Redox Homeostasis

Oxidative stress plays a role in the pathogenesis of many chronic diseases, by altering cellular redox balance. The ZnO nanocomposites prepared using the medicinal plants show the increased antioxidant activity with the synergistic effect of the ZnO nanoparticles, chitosan and phytochemicals. Phenolics and flavonoids, terpenoids and tannins act as natural free radical scavengers, donating electrons, hydrogen atoms, chelating metal ions which help to reduce the generation of reactive oxygen species (ROS). Due to controlled Zn^{2+} release, the activity of antioxidant enzymes, like superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), is increased and the expression of antioxidant genes is activated through the Nrf2/Keap1 pathway. Chitosan has been found to enhance the stability, dispersibility and bioavailability of nanoparticles, yielding higher antioxidant activity than that of the bare ZnO nanoparticles. Both antioxidant activity and reducing power assays were used to confirm the antioxidant activity of these nanocomposites, which offers potential application in oxidative stress disorders, wound healing and tissue regeneration (Gultekin et al., 2025; Ravi and Babu, 2025).

3.4 Anticancer Activity: Molecular Targets and Mechanistic Insights

The green-synthesized chitosan-mediated ZnO nanocomposites have been shown to be highly effective and selective anticancer agents that are biocompatible and have multifunctional therapeutic properties. Their anticancer activity is mostly related with the generation of reactive oxygen species (ROS), the regulation of Zn^{2+} release and modulation of the signaling pathway involved in apoptosis. After their internalization by the cell, the ZnO nanoparticles trigger oxidative stress, mitochondrial dysfunction, damage to DNA and activation of the intrinsic apoptotic pathway (Figure 3) via p53, Bax/Bcl-2 regulation, the release of cytochrome c and activation of caspases. They are also able to block key oncogenic pathways, such as PI3K/Akt/mTOR and NF-κB, which inhibit cell proliferation and induce apoptosis.

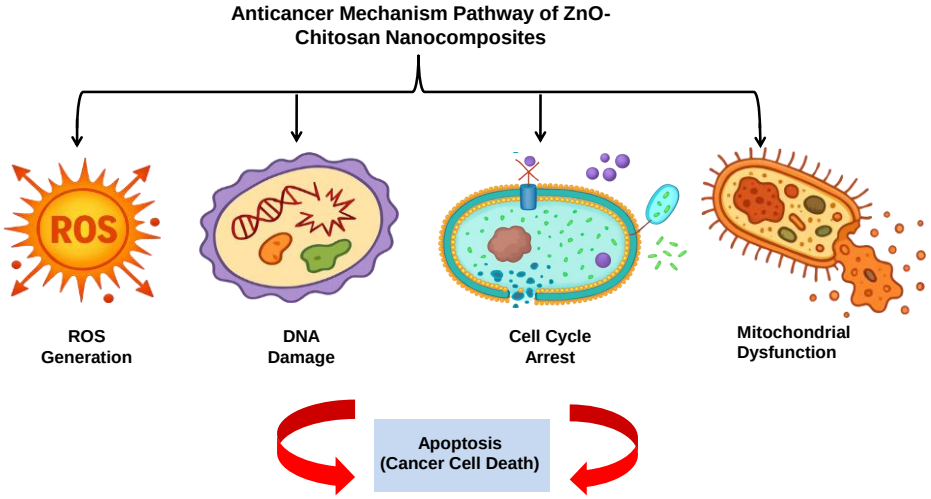

Figure 3: Mechanistic Insights to the anticancerous potential of Chitosan-Mediated ZnO Nanocomposites

Phytochemicals that are derived from plants also increase anticancer activity by synergistic antiproliferative and antiangiogenic activity, and chitosan provides enhanced stability of the nanoparticles, cellular uptake and intracellular drug delivery. These nanocomposites are found to exhibit strong cytotoxicity in various types of cancer cell lines such as breast, cervical, lung, liver, colon, prostate, ovarian, and glioblastoma cells. Although these encouraging results, more in vivo studies, pharmacokinetic evaluation, and long-term biosafety studies are needed to support their clinical conversion to targeted anticancer nanotherapeutics (Hussien et al., 2025; Konkal et al., 2026).

4. Future perspectives and research challenges

Green synthesized chitosan mediated ZnO nanocomposites exhibited excellent biomedical applications, but there are several limitations in their clinical applications. Plant sources and phytochemical composition can cause variations in the nanoparticles' reproducibility and biological performance, emphasizing the importance of standardized methods for their synthesis. Furthermore, detailed analysis of toxicity, biodistribution, pharmacokinetics, biodegradation and long-term biosafety are required for clinical translation. There is a need to explore Sub-Himalayan medicinal plants and pteridophytes as sustainable sources for green synthesis of nanoparticles in the future. A combination of metabolomics, omics technologies, artificial intelligence and high throughput screening could enhance optimization of synthesis and help to understand the mechanism. It is believed that these advances would aid in the development of the standardized chitosan-mediated ZnO nanocomposites which could be used in antimicrobial therapy, wound healing, tissue engineering, targeted drug delivery and cancer treatment (Chandrasekaran et al., 2022; Govea-Alonso et al., 2026).

5. Conclusion

ZnO nanocomposites prepared using medicinal plants and Sub-Himalayan ferns is a new type of multifunctional nanocomposites which have a wide range of biomedical applications. The synergistic effect of ZnO nanoparticles, chitosan and phytochemicals from plants increases the stability, biocompatibility and biological activity of these nanoparticles, which have the ability to kill bacteria, inhibit biofilm formation, and possess antioxidant and anticancer activity. These effects occur via membrane disruption, generation of Reactive Oxygen Species (ROS), regulated Zn^{2+} release and modulation of redox and apoptotic pathways. While showing promising preclinical results, there are challenges in the synthesis standardization, biosafety, and clinical validation. The development of safe, reproducible and clinically translatable chitosan-mediated ZnO nanocomposites for various therapeutic applications is expected to be made possible in the future by the development of green nanotechnology and biomaterial engineering.

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