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CRITICAL REVIEW

Recent advances in the synthesis, characterization and biomedical applications of zinc oxide nanoparticles

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Abstract

Zinc oxide nanoparticles (ZnONPs) have become the widely used metal oxide nanoparticles and drawn the interest of global researchers due to their biocompatibility, low toxicity, sustainability and cost-effective properties. Due to their unique optical and chemical properties, it emerges as a potential candidate in the fields of optical, electrical, food packaging and biomedical applications. Biological methods using green or natural routes are more environmentally friendly, simple and less use of hazardous techniques than chemical and/or physical methods in the long run. In addition, ZnONPs are less harmful and biodegradable while having the ability to greatly boost pharmacophore bioactivity. They play an important role in cell apoptosis because they enhance the generation of reactive oxygen species (ROS) and release zinc ions (Zn^{2+}), causing cell death. Furthermore, these ZnONPs work well in conjunction with components that aid in wound healing and biosensing to track minute amounts of biomarkers connected to a variety of illnesses. Overall, the present review discusses the synthesis and most recent developments of ZnONPs from green sources including leaves, stems, bark, roots, fruits, flowers, bacteria, fungi, algae and protein, as well as put lights on their biomedical applications such as antimicrobial, antioxidant, antidiabetic, anticancer, anti-inflammatory, antiviral, wound healing, and drug delivery, and modes of action associated. Finally, the future perspectives of biosynthesized ZnONPs in research and biomedical applications are discussed.

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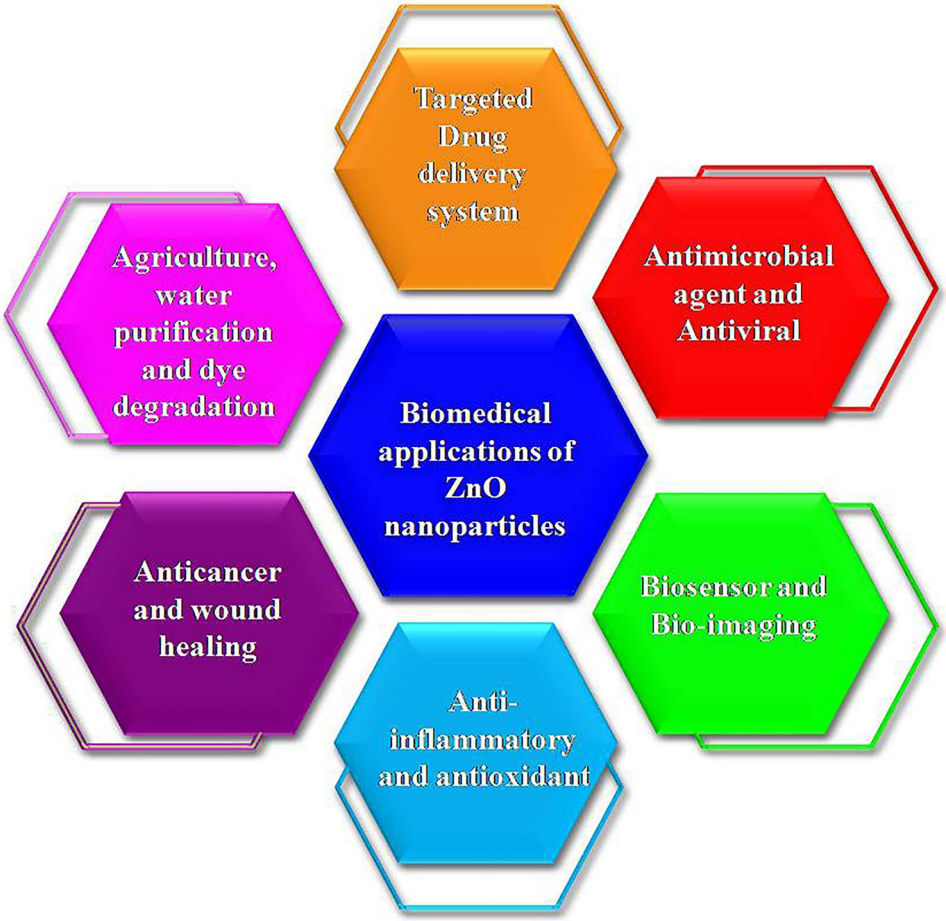
Graphical abstract



Keywords Zinc oxide nanoparticles · Biomedical applications · ROS generation · Mechanism of action

Introduction

During the last few decades, the interdisciplinary science "Nanotechnology" has revolutionized science and industrial technologies due to the presence of superior physicochemical or biological properties of nanoparticles (NPs) that are not present in their bulk form [1]. The greatest theoretical physicist at Caltech, Richard Feynman 1959, spread the idea of nanotechnology [2]. Nanoparticles have distinct key properties, such as a large surface area-to-volume ratio, enhanced thermal conductivity and electrochemical reactivity, and are regarded as a significant state of matter [3]. Recently, metal and metal oxide nanoparticles gained tremendous attention due to their promising applications in electronics, biosensors, photocatalyst, agriculture and biomedical fields [4]. The widespread use of NPs in biomedicine is due to their ability to interact with biological membranes, receptors, proteins and nucleic acids due to their small size [5]. The nanostructures exhibited targeted and long-term drug delivery with regulated drug-related toxicity. This technology has shown promise in the treatment of cancer, AIDS and an array of other ailments [6].

Our previous studies demonstrated the biological synthesis of selenium, silver, titanium dioxide and zinc oxide nanoparticles (ZnONPs) using cyanobacterial cell free extract [7–15]. Over various metal NPs, the inorganic metal oxide NPs exhibited remarkable biological applications even at low concentration, highly stable at high temperature and pressure due to their unique physicochemical properties [16]. Among the various metal oxide NPs like iron oxide (Fe_3O_4), copper oxide (CuO), titanium dioxide (TiO_2) and cerium dioxide (CeO_2), zinc oxide nanoparticles (ZnONPs) have gained scientific attention due to their biocompatibility, long shelf life and cost-effective nature [4]. ZnONPs possess distinctive optical and chemical properties with wide bandgap (3.37 eV) and high excitation binding energy (60 meV)

that enables its use in various biomedical, pharmaceutical and photocatalytic applications [17]. Moreover, Zn is an essential trace element present in human physiological system that confers its biocompatibility being less toxic and are highly biodegradable due to the soluble nature of Zn^{+2} ions [18]. It is abundant in many bodily tissues, including the brain, muscle, bone, skin and integral part of many enzyme systems. Zinc participates in the body's metabolic pathways and plays critical roles in protein and nucleic acid synthesis, hematopoiesis and neurogenesis [4]. Another property that makes ZnONPs as the potential candidate for biomedical applications is the presence of –OH group that allows it to dissolve slowly in acidic (e.g., cancer cells) and basic microenvironments [19]. However, due to its small particle size, nano-ZnO facilitates zinc absorption by the body and widely utilized as a food additive. Moreover, the US Food and Drug Administration (FDA) has approved ZnONPs as a generally-recognized-as-safe (GRAS) substance and nonhemolytic against human red blood [20]. In comparison with other metal oxide NPs, ZnONPs are more economical as well as less toxic and exhibit excellent biomedical applications. It has been reported that majority of pharmaceutically active compounds do not interact with zinc [4]. However, ZnONPs, both alone and doped with other metals, appear as a novel candidate used for tissue regeneration, implant coatings, bioimaging, wound healing, development of cancer therapies, targeted drug delivery, antimicrobials coatings or bandages, biosensors and gene delivery [21–23]. Rahman et al. [24, 25] demonstrated that ZnO and Mg/Cu-dual-doped ZnO exhibit good antibacterial activity against *Staphylococcus aureus* and *E. coli*, as well as radical scavenging properties when exposed to visible light. Ahmad et al. [26] synthesized gold-decorated hetero-nanostructured Au-ZnONPs utilizing *Carya illinoinensis* extract, which demonstrated maximal photocatalytic degradation of rhodamine-B dye (95%) within 180 min when compared to bare ZnONPs. Furthermore, Rahman et al. [27] also synthesized ZnONPs from aqueous leaf extract of *Ziziphus mauritiana Lam*., which demonstrated antibacterial efficacy against *Staphylococcus aureus* as well as antioxidant characteristics.

Use of ZnONPs in biomedicine is widespread due to their excellent biocompatibility, low toxicity (especially as anticancer and antibacterial), potent ability to trigger excess reactive oxygen species (ROS) production, release of zinc ions and induction of cell apoptosis [19]. Due to excellent luminescent properties, ZnONPs are one of the main candidates for bio-imaging [28]. Numerous studies support ZnONPs as the most advantageous metal NPs, with low toxicity and superior biocompatibility as the structural atom allocation being the most bioactive region highlights its pharmacological potency against a range of diseases [2, 4]. Taken together, the purpose of this review is to examine the processes used to synthesize ZnONPs while thoroughly comprehending their biological function. Even though ZnONPs have been the focus of an increasing number of studies, this review provides a detailed compilation of current advancements with simple examples to help readers better comprehend the significance of ZnONPs in biomedical research.

Approaches for synthesis and characterization of ZnONPs

Several synthesis approaches have been developed for ZnONPs and the choice of preparation depends on the specificity of application. Generally, two types of strategies were used—top-down and bottom-up approach, which comprises physical, chemical, and biological (green) synthesis of ZnONPs. The non-conventional methods include micro-fluidic reactor-based synthesis of nanomaterials. The top-down approach involves cutting or physically slicing the bulk materials into nano-sized materials [29]. On the other hand, bottom-up approach uses atoms or molecules for the fabrication of nanomaterials through chemical and biological synthesis. It is less expensive and quicker than the top-down strategy [30]. Different approaches for the synthesis of ZnONPs with their merits and demerits of these synthesis techniques are listed in Table 1. It is crucial to keep in mind that these procedures often require the use of harmful reducing agents and organic solvents, which are extremely reactive and hazardous to the environment [31]. However, green synthesis utilizes a range of biotic resources for the synthesis of ZnONPs, such as plants, bacteria, other biological elements including egg albumin, starch, proteins, gelatin and micro- or macroalgae that are listed in Tables 2 and 3 [32, 33]. Green sources are bio-molecules that act as capping and reducing agents during the synthesis of NPs, further stabilizing and influencing their characteristics [34]. Plants include several secondary metabolites and phytoconstituents that aid in the bio-reduction process during nanoparticle formation. It also played an important role in nanoparticle capping, which was essential for their stability and biocompatibility, and because of these molecules, no additional chemical reducing and capping agents were needed [2]. Microbial-mediated ZnONPs synthesis, on the other hand, offers an advantage over plant-mediated synthesis because microorganisms are easily replicated. The presence of numerous enzymes and biomolecules produced in the suspension or growth medium by microorganisms plays an important role in the bioreduction of NPs and contributes to the development of varied morphologies with mono- and polydispersed NPs [35]. However, there are numerous disadvantages associated with the isolation or screening of potential microorganisms, the usage of chemicals for growth medium, and the cost-effectiveness of synthesis procedures due to their

Table 1 Different methodologies used for the synthesis of ZnONPs

Synthesis Techniques		Merits	Demerits
Physical	Thermal evaporation Physical vapor deposition Ultrasonic irradiation Thermal/Laser ablation Arc plasma Sputtering Explosion processes Mechanical/Ball milling	Catalyst free Simple Industrial scale production	Parameter control Robust equipment High energy input Hampers crystallinity High cost Discharge instability
Chemical	Solgel processes Micro-emulsion Precipitation Atomic/molecular condensation Solvothermal method Chemical vapor deposition Spray pyrolysis Laser pyrolysis Aerosol pyrolysis	Low energy input Easy to handle chemical reagents Use of equipment Easy parameter handling Industrial scale production	Extensive use of surfactant High cost of precursors Toxic Low yield Low rate of deposition Low penetration Low solubility and mechanical instability
Biological	Microorganisms Plant extracts Biotechnology methods Biochemistry methods	Promising alternatives to both physical and chemical methods Environment friendly Non-toxic Use of inexpensive organic solvents Cost-effective Reproducible	Unclear mechanism Nanoparticle stability
Microfluidic reactor	Segmental flow Continuous flow Co-flow	High value-added products Reproducible	Parameter control

time-consuming nature. Consequently, plants are regarded as the most promising candidates for green synthesis, as they create more stable forms of the same than microbes.

Several biomolecules from plants or other green sources are combined throughout the green synthesis process to create stable and nontoxic ZnONPs. The overall procedure to produce ZnONPs using green sources is summarized schematically in Fig. 1.

The phytochemicals present in the cell extract function both as a stabilizing and as a capping agent for NPs to confer biocompatibility to NPs. High temperatures, high pressures, expensive equipment or hazardous materials are not needed for the process. The current, inexpensive and safe green synthesis of ZnONPs is preferable to the prior, expensive and hazardous techniques [102].

Following synthesis, nanomaterial characterization is necessary to learn about the physicochemical characteristics of the synthesized NPs, including their shape, crystal structure, defects, ionic strength, content and dielectric properties. Numerous studies imply that the form and surface chemistry of nanoparticles affect how safely and effectively they are distributed throughout biological systems (Fig. 2). With this, the polydispersity of materials makes it difficult to characterize NPs size, but it is crucial to understand the morphology because it is believed that the NPs size confers many of the unique properties for their use in nanomedicines [31].

Nanostructures cannot be resolved by optical microscopy; hence, electron microscopy is utilized to describe the nanoparticles. SEM (scanning electron microscopy) and TEM (transmission electron microscopy) are used to determine the morphology and size of NPs [104]. However, TEM is more frequently employed since it employs more potent electrons and provides high-resolution and informative image data about the shape, aggregation state, and distribution on an atomic scale. Energy-dispersive X-ray (EDX) analysis helps to determine the elemental composition and makes it easier to evaluate how synthesized nanoparticles are distributed in living tissues [105]. The 3D topography (height and volume) of NPs can be determined through atomic force microscopy (AFM) analysis [106]. Through the synthesis and capping of NPs, the simple and nondestructive Fourier transform infrared spectroscopy (FTIR) identifies the various metabolites and compounds [107]. The optical properties of colored samples are studied using UV–visible spectroscopy (UV–Vis), where reflectance data are used to

Table 2 List of biological sources used for the synthesis of ZnONPs

Biological source	Size (nm)	Morphology	Applications	References
Bacteria				
Bacillus megaterium (NCIM2326)	45–95	Rod and cubic	Antimicrobial	[36]
Halomonas elongate IBRC-M 10214	18.11–89.3	Multiform	Antimicrobial	[37]
Lactobacillus johnsonii	4–9	Spherical	–	[38]
Lactobacillus paracasei LB3	1179 ± 137	Spherical	Antimicrobial	[39]
Sphingobacterium thalpophilum	40	Triangular	Antimicrobial	[40]
Staphylococcus aureus	10–50	Acicular	Antimicrobial	[41]
Streptomyces sp.	20–50	Spherical	Antimicrobial	[42]
Acinetobacter schindleri S1Z1	20–100	Spherical	Antimicrobial	[43]
Bacillus licheniformis MTCC9555	250	Flower	Photocatalytic dye degradation	[44]
Psedomonas aeruginosa	35–80	Spherical	Antioxidant	[45]
Serratia ureilytica	170–600	Varied	Antibacterial	[46]
Lactobacillus plantarum VITES07	7–9	Spherical	–	[47]
Lactobacillus sporogens	145.7	Hexagonal	Antimicrobial	[48]
Aeromonas hydrophila	57.7	Spherical	Antimicrobial	[49]
Marinobacter sp. 2C8 and Vibrio sp. VLA	20.2 4.4	Hexagonal wurtzite	Antibiofilm, antioxidant	[50]
Fungi				
Aspargillusniger	40	Hexagonal	–	[51]
Phanerochaete chrysosporium	50	Hexagonal wurtzite	Antimicrobial cellulosic fabric	[52]
Dictyota dichotoma	80–100 µm	Spherical	Antibacterial and photocatalytic degradation	[53]
Candida albicans	25	Quasi-spherical	Synthesis of steroidal pyrazolines	[54]
Aspergillus fumigatus JCF	60–80	Spherical	Antimicrobial	[55]
Alternaria alternate	45–150	Spherical, triangular and hexagonal	–	[56]
Xylaria acuta	30–50	Rod and hexagonal	Antibiotic	[57]
Aspergillus fumigates	1.2–6.8	Oblate spherical and hexagonal	Agriculture	[58]
Aspergillus terreus	54.8–82.6	Spherical	Antifungal	[59]
Fusarium spp.	> 100	Triangular	–	[60]
Yeast				
Pichia kudriavzevii	10–61	Hexagonal wurtzite	Antimicrobial and antioxidant	[61]
Xylaria acuta	34–55	Hexagonal	Antimicrobial and anticancer	[57]
Pichia fermentas JA2	–	Smooth and elongated	Antimicrobial	[62]
Plants				
Deverra tortuosa	9.26–31.18	Hexagonal wurtzite	Cytotoxicity	[63]
Calliandra haematocephala	49.45	Nanoflowers	Photocatalytic dye degradation	[64]
Cassia fistulia	2.7	Spherical	Antibacterial	[65]
Citrus limon	37–40	Spherical	Antibacterial	[66]
Couroupita guianensis	–	Nanoflakes	Antibacterial	[67]
Melia azedarach	33–96	Hexagonal and spherical	Antioxidant and antibacterial	[68]
Citrus aurantifolia	50	Pyramid	–	[69]
Pongamia pinnata	30.4–40.8	Spherical wurtzite	Antimicrobial and cytotoxicity	[70]
Rosa canina	11–14	Spherical	Antibacterial	[71]
Lycopersicon esculentum	40–100	Spherical	Photovoltaic application	[72]
Ceropegia candelabrum	12–35	Hexagonal wurtzite	Antioxidant and antibacterial	[3]
Eclipta alba	3–9	Spherical	Antimicrobial	[73]
Crotalaria verrucosa	27–30	Hexagonal wurtzite	Antimicrobial and anticancer	[74]
Menta pulegium L	38–49	Spherical	Antibacterial	[75]
Moringa oleifera	12–30	Spherical and rod	–	[76]
Oak fruit hull	34	Spherical	Photocatalytic degradation	[77]

Table 2 (continued)

Biological source	Size (nm)	Morphology	Applications	References
Punica granatum	10–30	Spherical	Photocatalytic degradation	[78]
Myristica fragrans	66–70	Spherical	Antioxidant, antibacterial, antiparasitic and antidiabetic	[79]
Ocimum americanum	21	Spherical	Antioxidant and antimicrobial	[80]
Other biomolecules				
L-alanine	50–110	Spherical	– Antimicrobial	[81, 82]
Egg albumin	10–20	Spherical hexagonal wurtzite	–	[83]
Soluble starch	50	Spherical	Antimicrobial Antiviral	[84, 85]
Plasmid-DNA	32	Tetrapod	–	[86]
Alanine (Ala), threonine (Thr) and glutamine (Gln)	16	hexagonal wurtzite	Antimicrobial	[87]

investigate the surface plasmon resonance of metals and hypersensitive biological analysis [108]. The effects of the oxidative and reductive environments, phase transitions and thermal stability are determined by thermal gravimetric–differential thermal analysis (TG–DTA) [109]. To obtain size distribution information of molecules and particles majorly in the submicron region, DLS (dynamic light scattering) is very useful [110]. XPS (X-ray photoelectron microscopy) is a technique to analyze the surface chemistry of NPs that measures the empirical formula, chemical state and electronic state of the elements within the NPs. XRD (X-ray diffractometer) provides the information regarding the crystalline structure, phase identification and crystallite size [111].

Biomedical applications and mechanism of action of zinc oxide nanoparticles

ZnONPs have gained a lot of interest in a variety of biological sectors, including anticancer, antibacterial, antioxidant, antidiabetic, anti-inflammatory, drug delivery and many more.

Antibacterial activity

Due to the extensive use of antibiotics in human, animals and food, microorganisms develop antibiotic resistance. It is a worldwide phenomenon that is leading to the public health crisis. World Health Organization in 2001 had declared the antimicrobial resistance as international serious and urgent threats. Biogenic ZnONPs showed the rays of hopes for their use with standard antibiotics against multidrug-resistant bacteria [4]. Antibacterial activity of ZnONPs lies in their ability to induce oxidative stress. When bacterial cells encounter ZnONPs, they absorb Zn^{+}, interact with the thiol group of respiratory enzymes, inhibiting their action, affect the cell membrane and lead to ROS formation that damages the bacterial membranes, DNA and mitochondria, resulting in the death of bacterial cells (Fig. 3) [15]. Biogenic ZnONPs synthesized using different biological material showed varied antibacterial activity, e.g., Nur et al. [112], synthesized spherical-shaped ZnONPs (33 nm) by *Punica granatum* plant extract and showed a significant antibacterial activity against *E. coli* and *E. faecalis*.

ZnONPs derived from cyanobacteria *Oscillatoria sp.* extract exhibited dose-dependent inhibition in multidrug-resistant (MDR) bacterial strains (*S. aureus*, *B. cereus*, *E. coli* and *K. pneumoniae*) with lower MIC values of 62.5–125 µg ml^{-1} in comparison with commercially synthesized ZnONPs [14]. Jayabalan et al. [113] synthesized spherical-shaped ZnONPs (44.5 nm) using *Pseudomona putida* and presented antimicrobial activity against *Pseudomonas otitidis, Pseudomonas oleovorans, Acinetobacter baumannii, Bacillus cereus,* and *Enterococcus faecalis*. Fadwa et al. [114] showed the combination effect of colistin and ZnONPs (2 µg ml^{-1}) against *P. aeruginosa.* Tyagi et al. [115] showed that ZnONPs chemically conjugated with ciprofloxacin exhibited a 2.9-fold increase in antibacterial activity against *E. coli* and a 2.8-fold increase for *Streptococcus spp.* as compared to ciprofloxacin alone. ZnONPs conjugated with ceftriaxone and ampicillin exhibited significant antibacterial activity against gram-positive (*Staphylococcus aureus, Streptococcus pneumoniae* and *Streptococcus pyogenes*) and gram-negative (*Escherichia coli K1, Serratia marcescens* and *Pseudomonas aeruginosa*) bacteria [116].

ZnONPs synthesized using cyanobacteria *Gleocapsa gelatinosa* cell extract exhibited enhanced antibiofilm activity against MDR strains (*S. aureus*, *B. cereus*, *E. coli* and *K. pneumoniae*) with lower minimum biofilm inhibitory concentration (MBIC) values of 46.8 µg $ml^{-1}$and 93.7 µg ml^{-1}[15]. Flow cytometry analysis and confocal microscopy highlighted the strong interaction of ZnONPs

Table 3 Algal-mediated synthesis of ZnONPs

Algal strains		Size (nm)	Morphology	Applications	References
Cyanobacteria or blue green algae	*Nostoc sp. EA03* (Cyanobacteriaceae)	50–80	Star	Enhanced antibacterial, antibiofilm and anticancer	[88]
	Desertifilum sp. EAZ03	80–88	Rod	Antibacterial, antibiofilm and anticancer	[89]
	Anabaena strain L31 (Cyanobacteriaceae)	20–80	Spherical	Nontoxic sunscreen formulations	[1]
	Arthrospira platensis (Cyanophyceae)	30–55	Spherical	Antibacterial and anticancer	[90]
Green algae (*Chlorophyta*)	*Chlorella* (Chlorellaceae)	20 ± 2.2	Hexagonal wurtzite	Enhanced photocatalytic degradation of organosulfur pollutants	[91]
	Ulva lactuca (Ulvaceae)	10–50	Hexagonal, rod and triangle	Enhanced photocatalytic, antibiofilm and insecticidal activity	[92]
	Chlamydomonas reinhardtii (Chlamydomonadaceae)	55–80	Nanorod, nanoflower, porous nanosheet	Enhanced photocatalytic dye degradation	[93]
	Ulva lactuca (Ulvaceae)	~12	Nanocubes	Promising catalyst for production of biodiesel	[94]
Brown algae (*Pheophyceae*)	*Padina tetrastromatica* (Dictyotaceae)	16–30	Hexagonal wurtzite, rod, plate, star	Enhanced photocatalytic and high antibacterial activity	[95]
	Sargassum muticum (Sargassaceae)	42	Hexagonal wurtzite	None	[32]
	Alginate	20–40	Cubical or rod	Sensor—with high sensitivity and antibacterial activity	[96]
	Sargassum muticum (Sargassaceae)	30–57	Hexagonal	Antiangiogenic and antiapoptotic activity	[97]
	Sargassum wightii (Sargassaceae)	40–50	Spherical	Enhanced biofilm and immunosuppressant activity	[92]
	Sargassum wightii (Sargassaceae)	20–62	Spherical	Enhanced larvicidal and pupicidal toxicity on *A. stephensi and H. armigera*	[98]
	Sargassum myriocystum (Sargassaceae)	36	Spherical, radial, triangle, hexagonal, rod	Enhanced antibacterial activity against gram-negative bacteria	[99]
	Padina tetrastromatica (Dictyotaceae)	24–28	Varied	Enhanced antibacterial and UV protection activity	[100]
Red algae (*Rhodophyta*)	*Gracilariaedulis* (Gracilariaceae)	66–95	Rod-shaped	Effective anti-cancer activity against PC3cell lines	[101]

with intracellular components leading to biofilm destruction due to increased permeability, reduced exopolysaccharides secretion, altered bacterial growth and enhanced generation of intracellular ROS [15]. According to Badigera et al. [117] and Shkodenko et al. [118], smaller-sized NPs accumulate on the outer surface of the plasma membrane leading to increased surface tension and membrane depolarization by neutralizing surface potential for easier penetration into the cell. With the increasing concentration of ZnONPs, the penetration rate into the bacterial cell wall increased. ZnONPs after penetration into the cell through electrostatic interactions release Zn^{+2} ions, causing the conformational changes in enzymes that lead to the distortion of active sites, resulting in the inhibition of membrane proteins that disrupt the bacterial vital functions. In another study, Senthamarai et al. [119] synthesized ZnONPs (19.8 nm) from *A. marmelos* unripe fruit extract that showed enhanced antibacterial, antibiofilm and antioxidant agent. Furthermore Kappa-carrageenan-wrapped ZnONPs (KC-ZNONPs) exhibited antibacterial activity against MRSA strains, enhanced anti-inflammatory activity and were biocompatible with human RBCs [120]. The findings suggest that ZnONPs have a better antibacterial potential which is influenced by its dosage, treatment time and synthesis approaches. Additionally, increased antibacterial activity is caused by the surface area and size of particle variation, which are notable in biosynthesized ZnONPs.

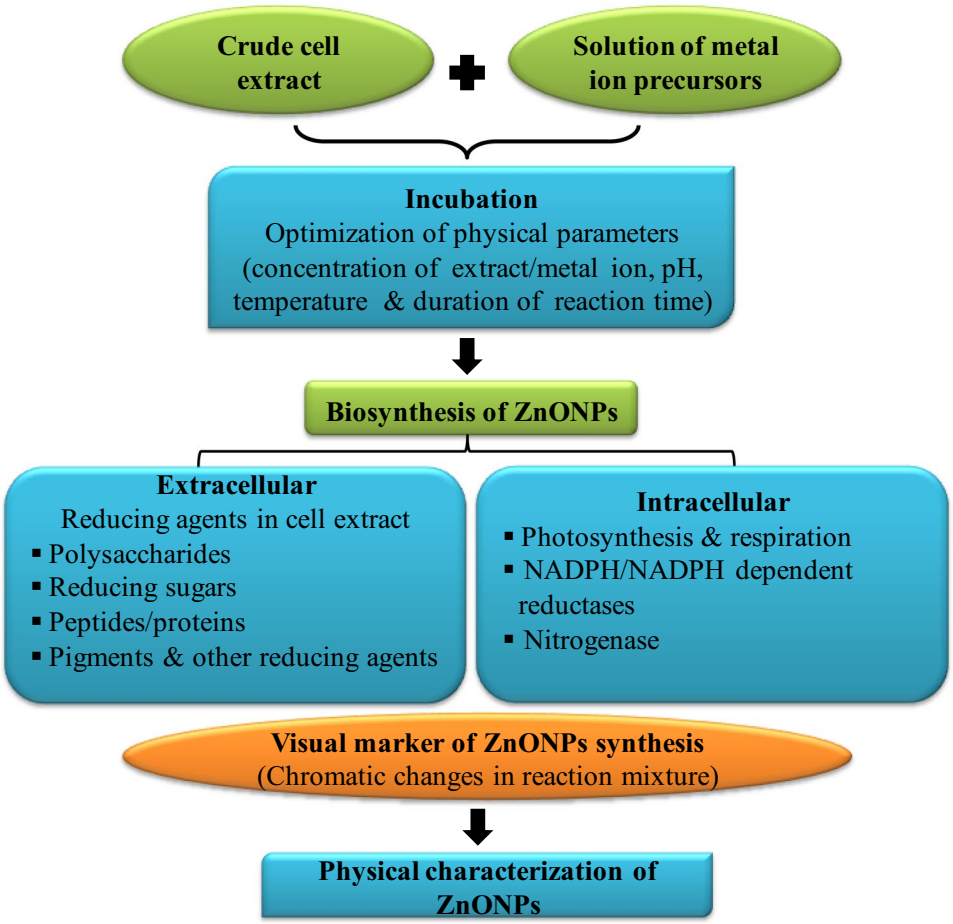


Fig. 1 Generalized pathway for the biosynthesis of ZnONPs using various green sources

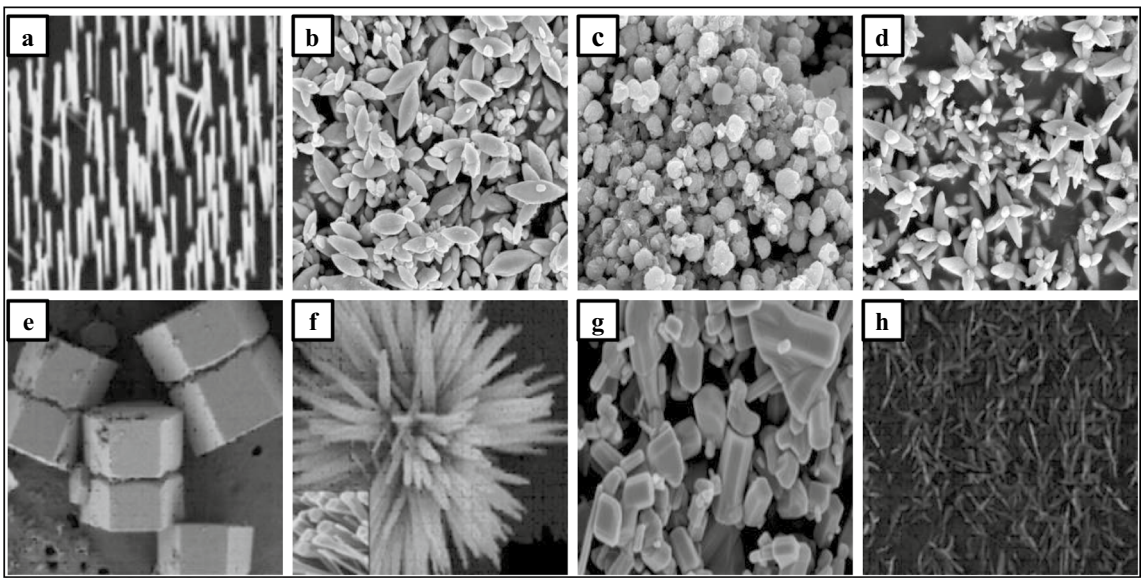


Fig. 2 Different morphology of ZnONPs: **a** needles and wires; **b** hexagonal; **c** spherical; **d** flower; **e** nanopellets or nanocapsules; **f** snowflake and dandelion; **g** square or rod; **h** helixes and springs. (Reprinted from [14, 103])

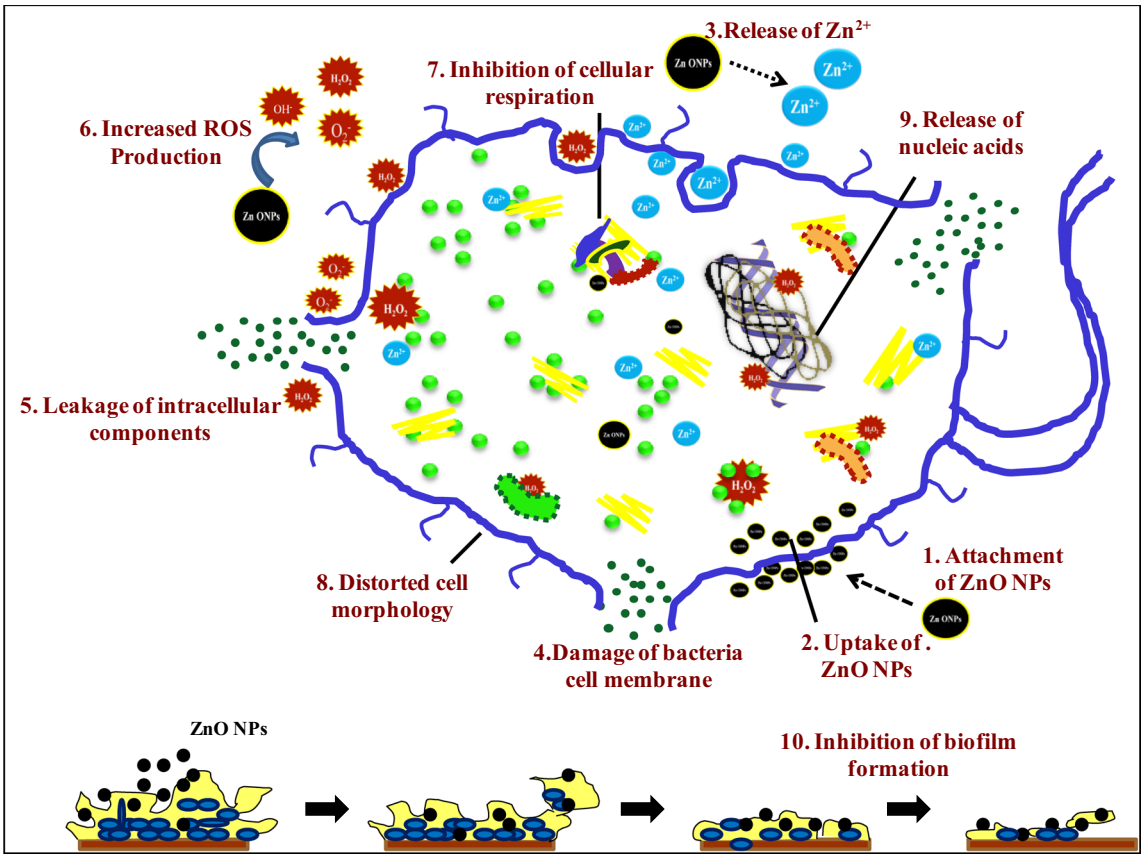


Fig. 3 A proposed schematic illustration of the various mechanisms induced by ZnONPs in bacterial cell inhibition

Applications of biogenic ZnONPs in food safety and agriculture have not yet been explored for future use [121].

Antifungal activity

ZnONPs have a promising antifungal activity that depends on their morphology, size, dose as well as source utilized in their biogenic synthesis. The antifungal potential of ZnONPs synthesized from leaf extract of *Crinum latifolium* inhibited the hyphal development and germ tube formation up to (34%) in *Candida albicans* [122]. On clinical isolates of *Candida sp*., the antifungal resistance of a 2% ZnONPs-based cold cream was greater than its antifungal efficacy [123]. ZnONPs from *Moringa oleifera* were toxic against two plant pathogens, *Alternaria saloni* and *Sclerrotium rolfii* [124]. ZnONPs synthesized using *Ziziphus nummularia* and *Prosopis farcta* extract exhibited antifungal activity against *C. albicans, C. glabrata* and *C. neoformans* with the lowest MIC values of 1.25 mg ml^{-1}[125, 126]. For ZnONPs that can enter fungal (conidial) cells by diffusion and endocytosis, the potential mechanisms of their antifungal activity begin with interference in mitochondrial function, encouragement of ROS generation and release of Zn^{2+} ions into the cytoplasm. ZnONPs can penetrate the nuclear membrane and produce excessive amounts of ROS and Zn^{2+} ions, which can lead to permanent DNA damage and cell death [127]. According to Lipovsky et al. [128], free radicals generated by ZnONPs are directly correlated with increased ROS productions, as well as a reduction in cell viability in *C. albicans* cells. Two mechanisms have been proposed for the antifungal action of ZnONPs. First is that ZnO in aqueous solution generates hydrogen peroxide (H_2O_2) from its surface, that can penetrate the cell membrane and kill them, inducing oxidative stress. Second is the release of zinc ions in medium with effects on active transport as well as on the amino acid metabolism [129]. Hajar et al. [130] showed the synergistic effect of ZnONPs with fluconazole against *C. albicans,* and Xue et al. [131] demonstrated the synergistic inhibition of *Phytophthora* growth by 0.25 g/L ZnONPs with 0.01 g/L thiram.

Antioxidant activity

Cell viability depends critically on oxidative metabolism as the generation of ROS and free radicals during this process may be able to overwhelm some enzymes, such as catalase, peroxidase and superoxide dismutase, leading to deadly effects on cells by damaging proteins, membrane

lipids, DNA enzymes, and interfering with cell signaling pathways [132]. Because they can produce lipid peroxides and other harmful free radicals, some oxidized foods are now linked to several serious illnesses, including hepatomegaly and necrosis of epithelial tissues, and a range of natural or synthetic antioxidants are used to combat these harmful free radicals but have disadvantages compared to today's biosynthesized NPs, such as high reactivity and toxicity [133]. According to Das et al. [134], the antioxidant potential of ZnONPs was caused by the transfer of electron density from oxygen to the odd electron situated at the nitrogen atom, in DPPH (2,2-diphenyl-1-picrylhydrazyl), with decreased strength of the n–π* transition at 517 nm. Many plants-derived ZnONPs are studied for antioxidant potential, e.g., Umar et al. [135] showed the hydrogen peroxide scavenging activity of ZnONPs in *Albizia lebbeck*. Mahendiran et al. [136] showed the (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) ABTS, 2,2-diphenyl-1-picrylhydrazyl (DPPH), superoxide and hydrogen peroxide scavenging activities of ZnONPs derived from *Aloe vera* and *Hibiscus sabdariffa*. In our previous investigation, we observed that *Oscillatoria*-derived ZnONPs had much higher antioxidant potential than commercially synthesized ZnONPs, with ABTS free radical scavenging activity ranging from 0 to 90% with an IC50 value of 54.2 µg ml^{-1} in comparison with ascorbic acid at 54.2 µg ml^{-1} that provides inhibition. It was observed that ZnONPs exhibited dose-dependent inhibition and the order of antioxidant activity was as follows: ABTS > DPPH > SOR > H_2O_2 [14]. Rehana et al. [137] also reported these scavenging activities in *Azadirachta indica* and *Murraya koenigii*. Hafez et al. [138] showed the in vivo antioxidant potential of ZnONPs (39.2 nm) supplemented with meal in broiler chickens at concentrations of 40 and 80 ppm that greatly boosted the activity of enzymes catalase and superoxide dismutase, which in turn decreased the levels of malondialdehyde (MDA).

The ZnONPs synthesized using *Azadirachta indica* leaf extract were investigated for their antioxidant potential by ferric reduction (FRAP) and DPPH radical scavenging assays. When ZnONPs (20 nm) were administered intravenously for 14 days at a dose of 100 ug, major bodily organs did not exhibit any discernible toxicity [139]. ZnONPs derived from *Camellia sinensis* leaf extract showed the antioxidant capacity in adipocytes, where ZnONPs exhibited cytoprotective efficacy against H_2O_2-induced oxidative damage (3T3L1) [140]. Japanese quails (*Coturnix japonica*) were fed dietary ZnONPs (40 nm) at a dose of 15–60 mg/kg for 60 days to examine its effects. It was observed that ZnONPs supplementation increased the cellular levels of GSH and mRNA levels of several antioxidant enzymes (SOD1, CAT, GPX1 and GPX7) in brain and liver tissues, which in turn reduced the lipid peroxidation. Aspartate aminotransferase and serum alanine aminotransferase activities, as well as the quantities of globulin, albumin and total proteins in the serum, were not significantly altered by the ZnONPs in comparison with the control group [141].

Anti-inflammatory activity

Inflammation is a part of body's defense mechanism by which the immune system defends body from harmful agents like bacteria, viruses, injuries and toxins to heal itself. An over-reactive inflammatory response is what triggers allergies and some autoimmune disease like arthritis. It has been demonstrated that the ZnONPs have anti-inflammatory properties because they suppress the expression of myeloperoxidase, the NF-pathway, the release of pro-inflammatory cytokines and mast cell degranulation [142]. Ilves et al. [143] investigated that ZnONPs were able to reach into the deep layers of the allergic skin and exerted higher anti-inflammatory properties by decreasing drastically pro-inflammatory cytokines (IL-10, IL-13, IFN-c and Th2 cytokines) in the mouse model of AD. Nagajyothi et al. [144] synthesized ZnONPs using the root extract of *P. tenuifolia* that exhibited significant anti-inflammatory activity by suppressing nitric oxide (NO) production as well as the related protein expressions of iNOS, COX-2, IL-1β, IL-6 and TNF-α in LPS-stimulated RAW 264.7 macrophages. However, aluminum-doped ZnONPs have been demonstrated to lower mast cell caspase-1 activation and thymic stromal lymphopoietin (TSLP) secretion, which in turn reduces the expression of pro-inflammatory cytokines such IL-1, IL-6 and TNF-α [145]. The capping of flavones such as isoorientin, orientin, isovitexin and vitexin by ZnONPs has been found to have a potent anti-inflammatory response in a myriad of areas, including by inhibiting cyclooxygenase, phospholipase A2 and lipoxygenases (enzymes that produce eicosanoids), which causes a decrease in leukotriene and prostanoids [146]. ZnONPs synthesized using two mangrove plants, *Heritiera fomes* and *Sonneratia apetala,* showed higher potential for anti-inflammatory (79%) in comparison with silver nanoparticles (69.1%) [147].

Anti-diabetic activity

Persistent hyperglycemia is a hallmark of the physiological condition known as diabetes. It has been found that zinc plays a significant role in the creation, retention and release of insulin. Additionally, it enhances insulin signaling by enhancing PI3K activity, tyrosine phosphorylation of insulin receptor, and suppression of glycogen synthase kinase [148]. The antidiabetic activity of ZnONPs has been explored because zinc has important role in insulin synthesis, storage, and secretion through mechanisms which increased PI3K activity, insulin receptor tyrosine phosphorylation, and inhibition of glycogen synthase kinase [149]. When compared

to other metal nanoparticles, ZnONPs are preferred for their antidiabetic benefits because of their higher cellular penetration, encouragement of glycolysis through hepatic glycogenesis, and increased insulin levels. These variables all work together to boost the expression of the GLUT-4 and INS genes. Additionally, it has synergistic effects on enhanced glucokinase expression and activity as well as IRA and GLUT-2 expression levels [150]. The potential benefits of ZnONPs (40 nm) were studied for 28 days at a dose of 10 mg/kg of ZnONPs orally in STZ-induced type-2 diabetic rats and observed dramatically reduced blood glucose levels while raising plasma insulin and pancreatic interleukin-10 (IL-10) levels. Additionally, ZnONPs reduced oxidative stress-related pancreatic damage by restoring the pancreas' total antioxidant capacity (TAC) and antioxidant defense system [151]. Similarly, in alloxan-induced diabetic rats, Bayrami et al. [152] investigated the anti-diabetic effects of biosynthesized ZnONPs with chemically synthesized ZnONPs utilizing *Urtica dioica* leaf extract. For 16 days, the diabetic rats were subcutaneously treated either with ZnONPs at a dose of 10 mg/dL or ZnO-extract at a dose of 8 mg/dL. By raising the level of insulin, biogenic ZnONPs exhibited superior antidiabetic potential in comparison with chemically synthesized and showed the reduced total cholesterol levels and elevated high-density lipoprotein cholesterol (HDLC) levels in diabetic rats. Wahba et al. [153] observed that ZnONPs effectively reversed diabetes-induced pancreatic injury by biochemical normalization of blood glucose and serum insulin. Further, El-Gharbawy et al. [154] and Kitture et al. [155] ZnONPs exhibited enhanced efficiency when tested in combination with the antidiabetic drugs, red sandalwood and vildagliptin. Furthermore, the α-amylase inhibitory activity of ZnONPs synthesized from floral extract of *Senna auriculata* [156] and leaf extract of *Andrographis paniculata* [157] was investigated for their antidiabetic potential that showed the lower IC50 value of 121.42 μg ml^{-1}&149.65 μg ml^{-1}. In addition, ZnONPs synthesized from *M. fragrans* and *Withanias omnifera* extracts were shown to have an excellent α-amylase (73%; 90%) and α-glucosidase (65%; 95%) inhibition, suggesting that they have potential antidiabetic action [79, 158].

Anticancer activity

Cancer is the deadliest disease that develops due to the uncontrolled growth of cells. By 2040, it is anticipated that there will be 29.5 million new instances of cancer diagnosed each year and 16.4 million cancer-related deaths [159]. Cancer persists despite long-run traditional therapeutic approaches and technological developments and has extensive drawbacks, e.g., reduced bioavailability, adverse health effects and high cost make their use limited [2]. It is well renowned that anticancer drugs disrupt the mitochondrial electron transport chain causing increased generation of ROS leading to the impaired mitochondrial and protein activity causing cell death [160]. Due to their capacity to release dissolved zinc ions into the cells, ZnONPs promote ROS generation and activate the apoptotic signaling pathway [161]. Zinc is crucial for the expression of the oncogene p53, which regulates apoptosis by controlling the activity of Caspase-6 enzyme [4]. In addition, the unique electrostatic feature of ZnONPs enables them for selective targeting of cancer cells. An abundance of anionic phospholipids causes electrostatic attraction between ZnONPs and cancer cells, which promotes cancer cells to take up ZnONPs causing cytotoxicity [162]. According to Sana et al. [74], small size of ZnONPs facilitates their permeation and retention inside tumor cells, where they can act. The potential mechanisms underlying the targeted cytotoxicity of ZnONPs against cancer cells are, when exposed to an alkaline intracellular condition, ZnONPs dissolve release Zn^{2+} ions leading to an increased generation of ROS in cancer cells compared to normal cells initiates the intrinsic mitochondrial apoptotic pathway causing cell death in cancer cells. The molecular mechanism underlying ZnONPs cytotoxicity comprises the generation of ROS to significantly increase oxidative stress, DNA damage and disruptions on cellular lipids and proteins are summarized in Fig. 4. Moghaddam et al. [61] synthesized ZnONPs using *Pichia kudriavzevii* GY1 that exhibited cytotoxicity against breast cancer MCF-7 cells by apoptosis. ZnONPs-induced apoptosis was mainly through extrinsic/intrinsic apoptotic pathways and down-regulation of antiapoptotic genes of Bcl-2, AKT1, and JERK/2 with up-regulation of proapoptotic genes of p21, p53, JNK, and Bax. ZnONPs synthesized from leaf extract of *Raphanus sativus* exhibited the higher anticancer potential on treated A549 cell lines [163]. It has been extremely difficult for a drug to be classified as anticancer without being able to distinguish between cancerous and normal cells, as lack of selectivity can cause harmful effects.

Numerous studies have shown ZnONPs preference toward malignant cells. According to Chandrasekaran et al. [164], ZnONPs selectively induce apoptosis in C2C12 myoblastoma cancer cell with increased caspase-3 (CASP3) enzyme activity and ROS generation in comparison with 3T3-L1 adipocytes. In another study, ZnONPs (47.2 nm) synthesized from aqueous leaf extract of *Laurus nobilis* exhibited the cytotoxicity against human A549 lung cancer cells at concentrations of 80 μg ml^{-1} and showed no effect on normal murine RAW264.7 macrophage cells [165]. Along this line, Wahab et al. [166] showed that ZnONPs were most toxic against T98G cancer cells, moderately toxic against KB epithermoids cells and least effective against normal human HEK cells.

Even though many of treatments have a poor therapeutic index, several routinely given medications can slow down

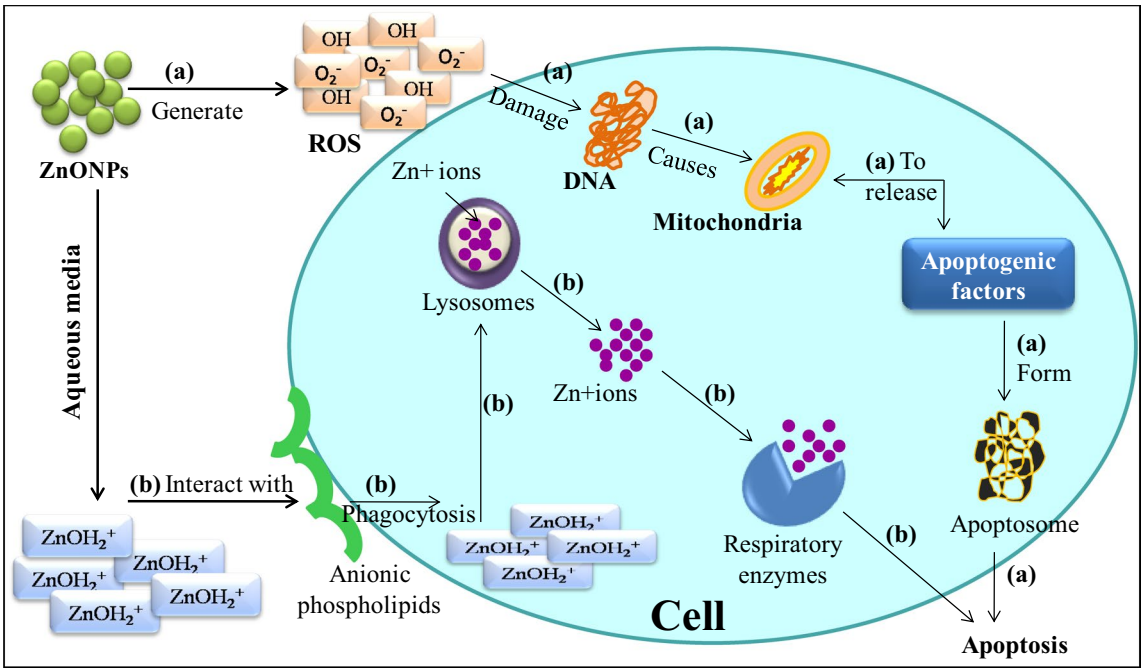


Fig. 4 Mechanism of action of ZnONPs; **a** reactive oxygen species (ROS) generation induced by ZnONPs causes DNA damage, apoptogenic substances get released from mitochondrial membrane forming the apoptosomes leading to apoptosis; **b** at lower pH protons from local environment moved to the surface of negatively charged ZnONPs creating a positively charged surface ($ZnOH^{2+}$), that enters the cell due to their interaction with negative phospholipids on the cell's outer membrane and after dissolving in acidic lysosomes, ZnONPs release Zn^+, that inhibits the respiratory enzymes leading to cell death

the rate at which cells divide. Sharma et al. [167] and Hackenberg et al. [168] showed that the cytotoxicity of chemotherapeutic agents like doxorubicin (DOX), cisplatin (CPT) and paclitaxel (PTX) increased significantly in combination with ZnONPs. ZnONPs in combination with sorafenib exhibited significant anticancer activity against Ehrlich carcinoma cells in mice with an effective decrease in tumor weight/tumor cell viability and a significant increase in DNA fragmentation, generation of reactive oxygen species and expression of the apoptotic gene caspase-3 in the tumor tissues [169]. ZnONPs conjugated with L-asparaginase from *Aspergillus terreus* exhibited significant anticancer activity against MCF-7 cell line that decreased 35% viability of cancer cells [170].

Wound healing activity

The largest organ in the body, the skin, shields us from outside threats and develops wounds when damaged. Healing from a wound takes patience, and microbial infection (*P. aeruginosa* and *S. aureus*) may slow down the process [171]. Metal oxide nanoparticles have the potential to get rid of pathogenic species and hasten wound healing. Biogenic ZnONPs showed huge potential as a wound-healing agent for the treatment of normal injuries and open wounds [172]. Owing to the strong antimicrobial properties, ZnONPs have been successfully used in wound dressings. ZnONPs synthesized using *Aloe barbadensis* leaf extract showed the healing efficiency of ZnONPs/silica gel dressings (30 ppm) in mouse wounds within 11 days in comparison with control [173]. Biosynthesized ZnONPs using *Prosophisfracta* and coffee can penetrate cotton wound bandages, resulting in patches with a potent antibacterial action. As a result, they may be used to treat and cover wounds that are prone to infection, like burns or diabetic sores [174]. According to Raguvaran et al. [175], ZnONPs-loaded sodium alginate-gum "Acacia hydrogels" (SAGA-ZnONPs) showed the wound healing effects in sheep fibroblast cells. Rayyif et al. [176] demonstrated the fabrication of nano-coated wound dressing containing ZnONPs that impair bacteria viability of chronic wounds after 6 h of contact in a dose-dependent manner and maintained for up to 3 days. Karahaliloglu et al. [177] combined chitosan/ silk sericin scaffolds with lauric acid and ZnONPs. The diameter of zone of inhibition increased from 2 to 7 mm for *E. coli*, and 2.5 to 6 mm for *S. aureus* after treatment of ZnONPs. According to Soubhagya et al. [178], bio-nanocomposite-based 3D chitosan/pectin/ ZnONPs porous films showed nil cytotoxicity, cell growth and migration, or adverse effects on primary human dermal fibroblast cells (HFCs), referring to a safe biomaterial for accelerating wound healing. In addition, azithromycin-doped ZnONPs impregnated into an HPMC gel by Saddik et al.

[179] exhibited the improved bacterial eradication and epidermal repair, which in turn stimulated tissue development and expedited the healing of the infected lesion. Manuja et al. [180] demonstrated similar potential for accelerating healing by ZnONPs hydrogels synthesized from sodium alginate gum acacia that left no scar at the rabbit skin excision wound.

Antiviral activity

Numerous viruses, including hepatitis C and E virus (HCV, HEV), herpes simplex virus (HSV), human papillomavirus (HPV), human immunodeficiency virus (HIV) and severe acute respiratory syndrome coronavirus (SARS-CoV), have been shown to be significantly inhibited by ZnONPs. The antiviral evaluation of ZnONPs synthesized from *Plumbago indica* leaf extract revealed that they showed remarkable activity against herpes simplex virus type 1 (HSV-1), with CC50 and IC50 values of 43.9 and 23 μg ml^{-1}, respectively, in comparison with acyclovir, which at 1 μg ml^{-1} offered 100% complete immunity against HSV-1 [181]. A study by Ghaffari et al. [182] reported that PEGylated ZnONPs and ZnONPs exhibited higher inhibition rates of 94.6% and 52.2%, against H1N1 influenza virus. It caused a remarkable reduction in fluorescence emission intensity in PEGylated ZnONPs-treated cells with lower cytotoxicity on MDCK-SIAT1 cells and concluded that PEGylated ZnONPs may be an efficient and promising antiviral treatment for H1N1 influenza virus infection. According to TeVelthuis et al. [183] and Erk et al. [184], the toll-like receptor signaling pathways and proteins downstreaming are the action mechanisms underpinning the antiviral efficacy of ZnONPs, which in turn promote the innate and adaptive immune response leading to the generation of pro-inflammatory cytokines that impede the virus. Zn^{2+} ions have antiviral capabilities by inhibiting virus proliferation, packaging and expulsion during its life cycle, causing reactive oxygen species generation, and preventing infection. In addition to blocking viral RNA-dependent RNA polymerase activity, zinc also alters the host immune response to prevent viral invasion and inhibits viral replication and the translation of viral polyproteins [183]. However, ZnONPs have the ability to dissolve water molecules, release Zn^{2+} ions and absorb UV–Vis light, producing ROS like H_2O_2 and OH^- free radicals [185, 186]. ZnONPs have been shown to inhibit both SARS-COV and retrovirus in vitro RNA polymerase activity, and zinc ions inhibit virus replication in cell culture [183]. The molecular mechanism underlying ZnONPs toxicity against SARS-CoV-2 virus involves the generation of ROS that significantly increase oxidative stress; RNA degradation and disruptions on cellular proteolysis are summarized in Fig. 5. ZnONPs impede SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) via altering template binding during the elongation stage of RNA translation. Furthermore, ZnONPs inhibit membrane fusion by interacting with the histidine residue of viral E1 protein, which obstructs the viral polyprotein proteolytic mechanism in turn inhibiting the viral integration [187]. Collectively, ZnONPs serve as a prospective candidate for their use in nanomedical viral-targeting therapy for the SARS-COV virus owing to

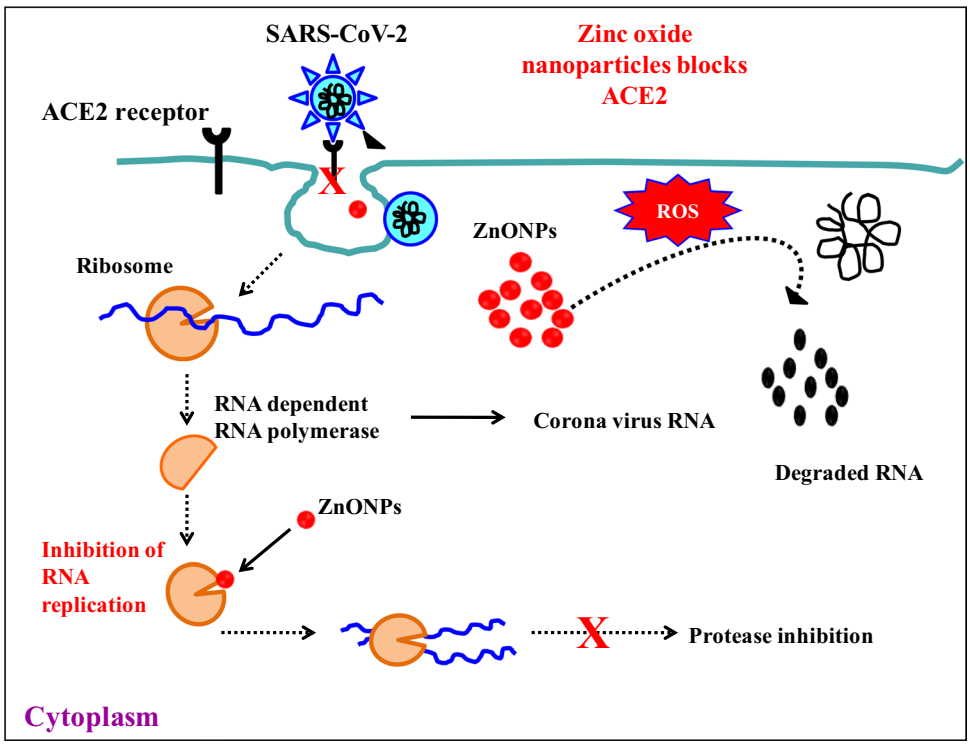


Fig. 5 Mechanism of action of ZnONPs antiviral activity against SARS-CoV-2 virus

its inertness to an array of medicines and persistent visible fluorescence. Recently, El-Megharbel et al. [188] observed that ZnONPs had remarkable antiviral activity against SARS-CoV-2 with an IC50 value of 526 ng $ml^{-1}$and cytotoxic levels with a CC50 value of 292.2 ng ml^{-1} against VERO-E6 cells. Additionally, it was found that ZnONPs-enhanced generation of ROS causes damage to the SARS-CoV-2 membrane proteins. Jana et al. [189] showed that polysaccharide-encapsulated ZnONPs exhibited remarkable antiviral activity against human cytomegalovirus (HCMV), with cell survival rates of 93.6% and 92.4% at 400 µg ml^{-1}. Gupta et al. [190] investigated the antiviral efficacy of both ZnONPs and tetrapod-shaped ZnO(TP) against hepatitis E and hepatitis C viruses. Both showed significant antiviral activity, but ZnO(TP) were more effective and showed no cytotoxicity even at higher doses as compared to control.

Application of ZnONPs in drug delivery

Drug delivery using ZnONPs has emerged as an incredibly efficient approach for treating various illnesses, such as cancers. Because of their cheap fabrication from inexpensive metal precursors, biocompatibility and efficient cellular absorption via endosomes, ZnONPs have been suggested as a feasible prospect for targeted drug delivery. The pH-dependent release of the targeted drug and ZnONPs into the cytoplasm that occurs through receptor-mediated endocytosis is the underpinning mechanism behind the increased cytotoxic potential of anticancer drug-loaded ZnONPs [191]. Additionally, the excessive generation of ROS and Zn^{2+} ions from ZnONPs results in the apoptosis of cancer cells [2]. Biologically synthesized doxorubicin-loaded ZnONPs using *Borassus flabellifer* extract exhibited dose-dependent cytotoxicity against human breast cancer (MCF-7) and colon cancer (HT-29) cell lines with an IC50 value of 0.125 µg $ml^{-1}$and displayed low cytotoxicity in the murine model system, according to the in vivo toxicity evaluation [192]. Using chitosan-coated ZnONPs synthesized from ethanolic leaf extract of *Camellia sinensis*, Akbarian et al. [191] fortunately loaded paclitaxel (PTX) and observed the enhanced cytotoxicity against malignant MCF-7 cell lines without being nontoxic on healthy fibroblast cell lines. According to Yuan et al. [193], ZnO quantum dots loaded with chitosan were used to deliver anticancer drug doxorubicin to HeLa cells.

Applications of ZnONPs in bioimaging

The inherent photoluminescence properties of ZnONPs make them a suitable candidate for biosensing applications. Their chemical structure consists of hydroxyl (−OH) groups, which makes it easier to dissolve in a basic and acidic environment especially in a tumor microenvironment for efficient imaging [4]. Jiang et al. [28] used ZnO nanosheets for imaging the leukemia K562 cells and observed the clear yellow orange light emission around or inside the cells under UV excitation, suggesting the successful penetration of the cells by these ZnO nanosheets. Pan et al. [194] used photoluminescent ZnO@polymer core–shell NPs for mouse imaging via intradermal and intravenous injections. According to Sudhagar et al. [195], green, fluorescent ZnONPs conjugated with transferrin were involved in cancer cell imaging with lower cytotoxicity. Singh et al. [196] doped zinc oxide quantum dots (QDs) with Gd and observed an increase in the emission intensity and lower toxicity to HeLa cancer cells, imaged with confocal microscopy. Furthermore, many studies had reported the use of ZnONPs in bioimaging like., use of ZnONPs for skin tissue architecture [197], ZnO nanocrystals in KB cells [198], CdSe(S)/ZnO-QDs in *S. oneidensis* [199], ZnONPs in human skin and rat liver cells [200], ZnONPs in plant tissue cell implosion [201] and ZnONPs in blood cells of zebrafish and roots/shoots of *Arabidopsis* [202].

Application of ZnONPs in tissue engineering

Due to their antineoplastic, angiogenic, UV scattering, antioxidant, collagen production, bio-mineralization and wound-healing characteristics, ZnONPs have become alternative biomaterial for tissue engineering and regenerative medicine applications [203]. They can aid in promoting tissue repair while lowering immunogenicity and preventing illness. For tissue engineering and regenerative medicine applications, ZnONPs are reported to stimulate cell growth, proliferation, transformation and metabolic functions in a numerous cell line [204]. As evidenced by in vitro and in vivo approach, the application of biogenic ZnONPs in tissue engineering has grown even more specific due to its proangiogenic features that may be incredibly beneficial in improving the integration of sophisticated biomaterials into host tissue. Yousefi et al. [205] investigated the ZnONPs/chitosan tubular scaffold for tendon restoration in a rabbit model and observed complete absorption of scaffold at repair site after eight weeks of treatment. It also prevented the formation of adhesions and infections around the tendon with enhanced angiogenesis and collagen fibril rearrangement, pointing to its promising use in the treatment of tendon acute injuries. Shubha et al. [206] showed that biosynthesized ZnONPs using gallic acid isolated from the aqueous extract of *Phyllanthus emblica* exhibited less toxicity than clinically recommended ZnONPs and observed noticeable results in 3T3 fibroblasts from Balb mice, which suggested its use near connective tissue cells because they are benign to cells. Using the stem extract *Artemisia annua*-derived

ZnONPs, Wang et al. [207] showed the impact of ZnONPs on bone regeneration inMG-63 Cells. Without significantly increasing cytotoxicity, biogenic ZnONPs demonstrated improved osteoblast proliferation, differentiation, collagen production and calcium mineralization. According to a study by Shafique et al. [208], *Cymbopogon citratus* leaf extract derived ZnONPs exhibited the promising callogenesis and regeneration frequency in *Panicum virgatum* nodes and internodes. It was confidently expected that this exploration would advance tissue culture technology by increasing the rate of plant in vitro regeneration in various species. Heidari et al. [209] and Harikrishnan and Sivasamy [210] reported the efficacy of nanohydroxyapatite/ZnO (HA/ZnO) scaffolds and polycaprolactone/ZnO(PCL-ZnO) scaffolds for bone tissue regeneration in human osteoblast cells. Improved biocompatibility and biosorption properties were demonstrated by the HA/ZnO scaffold, whereas PCL/ZnO scaffolds offer a nano-porous matrix for improved cell adherence and higher cell proliferation. Furthermore, Forero et al. [211] showed the potential efficacy of nano-copper-zinc alloy (nCuZn) containing chitosan/gelatin/nano-hydroxyapatite (Ch/G/nHAp) scaffold in bone tissue regeneration and observed scaffolds-induced osteogenesis and increased mouse embryonic fibroblast proliferation and adhesion (MEFs). The scaffold promoted the growth of the surrounding tissues after in vivo implant, encouraging the formation of granulation tissue.

Future perspectives

ZnONPs demonstrate superior attributes to bulk materials because of its small size and high surface area-to-volume ratio, due to which they are being investigated in a variety of disciplines, including the biosensor, agriculture, cosmetic and food industries. Biologically synthesized ZnONPs have gained significant attention due to their eco-friendly, simple, and economical nature, which allows producing NPs on a big scale. Biomolecules present in cell extract facilitates the reduction and stabilization of synthesized ZnONPs and exhibited enhanced antimicrobial, anticancer, anti-inflammatory, drug delivery, bioimaging along with other biomedical applications. The capacity of the ZnONPs to increase the bioavailability of therapeutic drugs while acting as drug carriers to increase therapeutic efficacy has also long been acknowledged. Many critical variables must be dealt with in the future for the reliable and efficient production of ZnONPs for innovative applications. Modulation of various variables such as pH, temperature, salt precursor and extract concentration should be explored for efficient regulation of particle size distribution and morphology for economically feasible ZnONPs fabrication on a large scale in order to meet future demands. With the growing prevalence of ZnONPs, researchers should examine their buildup in the surroundings and possible long-term impacts on humans and animals. Furthermore, ZnONPs may be modified by biomolecules such as polysaccharides and proteins to boost persistence and their biocompatibility as these organic compounds have properties similar to human tissue.

Conclusion

The ZnONPs are promising candidates for biological applications due to their intrinsic toxicity of ROS generation, activating apoptotic signals within the cells to hinder both microbial pathogens and malignant cells. The present review highlighted the green synthesis of ZnONPs, to get over the limits of traditional chemical and physical techniques and its use in various biomedical applications. It emphasizes how the use of biogenic ZnONPs in drug administration, nanomedicine and cure can open up new avenues for giving more customized, safer and efficient therapeutic options for tumors and HIV/AIDS, as well as noninvasive diagnostics and nutraceutical delivery. Researchers will eventually be able to deliver medications for a greater duration of time with enhanced accuracy and penetration by manipulating size of NPs and surface characteristics. Furthermore, in vitro and in vivo studies are anticipated to explain the cellular level mechanism of action, with significance in numerous biomedical diagnostics and therapeutic disciplines. As a result, rapid progress in the application of biologically synthesized ZnONPs is expected in the future decades.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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