



# Biogenic Zinc Oxide Nanoparticles and Their Biomedical Applications: A Review

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## Abstract

Nanotechnology has inscribed novel perception into the material science and one of the most extensively used nanomaterials is Zinc oxide nanoparticles (ZnO NPs) with healthcare and biomedical applications. Because of its outstanding biocompatibility, low toxicity, and low cost, ZnO NPs have become one of the most prominent metal oxide NPs in biological applications. This review highlights the different aspects of ZnO NPs, like their green synthesis as a substitute of conventional route due to avoidance of threat of hazardous, costly precursors and subsequent mostly therapeutic applications. Due to their wide bandwidth and high excitation binding energy, ZnO NPs have undergone extensive research. In addition to their potential applications as antibiotics, antioxidants, anti-diabetics, and cytotoxic agents, ZnO NPs also hold a promising future as an antiviral treatment for SARS-CoV-2. Zn has antiviral properties and may be effective against a variety of respiratory virus species, particularly SARS-CoV-2. This review includes a variety of topics, including the virus's structural properties, an overview of infection mechanism, and current COVID-19 treatments. Nanotechnology-based techniques for the prevention, diagnosis, and treatment of COVID-19 are also discussed in this review.

**Keywords** Nanotechnology · ZnO NPs · Biogenic synthesis · Bio-medical applications · SARS-CoV-2

## 1 Introduction

Nanotechnology has driven a scientific attention due to its ability to produce materials on a nanoscale (up to 100 nm). Nanoparticles (NPs) have discrete optical, mechanical, catalytic, and biotic proficiencies over their bulk complements due to their enormously tiny size and high surface area to volume ratio. Due to their distinctive features and widespread application potential, metal oxide NPs have fascinated a lot of scientific consideration [1]. Zinc oxide nanoparticles (ZnO NPs) have been broadly examined for practice in a variety of applications among metal NPs due to their optical, piezoelectric, semiconducting, spintronic, and photonic abilities. ZnO NPs are indispensable wide and straight band gap semiconductors (3.37 eV). One of the most notable features of ZnO NPs is its high excitonic binding energy (60 meV), which permits it to function well in optical systems at or overhead room temperature [2].

ZnO nanoform have been established to be a subsequent generation, lucrative anti-septic, contributing in evolving nanotechnology applications such as electronics, chemical detecting devices, solar cells, anti-microbes, water medication automations and is accomplished of being used in sunscreen and cosmetics because of having UV absorbing properties [3]. Zinc oxide is of appreciable economic and industrial choice due to various ranges of properties that makes it applicable in several different fields, such as in rubber industries, metallic surface treatment and biomedical areas [4].

Among the many qualities of zinc oxide (ZnO), its anti-bacterial activity, UV absorption properties, semi-conductivity, and vulcanization stimulator are its standout traits [5]. Several reports have studied and employed ZnO for photo-catalysis [6] as an antimicrobial agent [7], in energy cells [8] and in sensors [9]. The current use of ZnO NPs in biomedical engineering includes bio-imaging, wound healing, implant coating, tissue engineering, and creation of anti-cancer medicines [10]. ZnO NPs have received the most attention among all NPs due to their benefit of having high biocompatibility with human cells. ZnO NPs exhibit direct antiviral efficacy against many viruses due to their

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capacity to block viral entrance, replication, and spreading throughout the organ, ultimately causing viral death due to the activation of reactive oxygen species, which causes oxidative stress [11]. From last few years, development of environmentally friendly products and processes has gained attention due to the concern related to climate change, various types of pollution, limited natural resources, and human health-related issues among others [12]. As a consequence, researchers are working on developing alternative methods for improving production of metals and their respective oxides using biological materials [13]. This biogenic or green production of metal oxide NPs has been explored by many research groups to replace the chemical and physical methods used in various industries. Although a substantial amount of research has been outlined in this area, the actual mechanism of formation of the NPs obtained by green synthesis is still not fully known and understood due to large complexity of the biological material used for preparation. In this context, this review highlights the current advancement in the green synthesis of ZnO NPs, and giving attention on distinct methodologies of formation mechanism of NPs.

## 2 Synthesis of Zinc Oxide Nanoparticles

The different approaches for the formation of ZnO NPs other than green synthesis are chemical and physical methods. Sol–gel, chemicals reduction, precipitation, and hydrothermal procedures consist of some of the chemical approaches that can involve significant energy consumption and require high pressure or temperature conditions to generate NPs [14]. Sol gel method is the most prominent method in chemical synthesis in which zinc salt precursor is nitrate, sulphate, chloride, etc. and is the chemical reagent in order to regulate the solution pH, as well as avoid the precipitation of  $\text{Zn}(\text{OH})_2$ . The next step for this method is the heating of the solution in high pressure or at temperature up to 1000 °C to finally obtain  $\text{Zn}(\text{OH})_2$  [15]. At the time of synthesis, addition of some chemical stabilizing agents such as citrate polymer (like polyethyleneglycols, polyvinylpyrrolidone and amphiphilic block copolymers) can control the size and agglomeration of ZnO NPs [16]. Moreover, the concentration of chemicals used during synthesis influences the shape and size of NPs and it is the most significant factor considered in chemical synthesis. In comparison, a physical method is more rarely used in use than chemical methods but ZnO NPs can be formed via physical techniques by ultra sonication, plasma and vapor deposition [17]. Nevertheless, all these physical techniques usually demand complex equipment and high energy consumption that ultimately ends up with high cost of the outcomes. One additional approach

for the generation of ZnO NPs exploits biological samples, which has grown as possible eco-friendly processes.

### 2.1 Green Synthesis of Zinc Oxide Nanoparticles

In the last two decades, there has been a growing interest in the production of ZnO NPs via biological methods. The fact that this novel technique avoids using hazardous chemicals or requiring a lot of energy through biological synthesis makes it more practical, environmentally benign, and economically viable [18]. The different reports in literature suggest that green synthesis of metal and their oxides NPs is more convenient for environment than the different conventional approaches currently used [19]. This work has primarily been done on a laboratory scale, but commercial usage is expected in the up-coming future because of heavy equipment is not required and major progress has been made in considering the composition of biological extracts and their interactions with metal ions [20]. By introducing biological substrates like plants, bacteria, fungi, and algae as chemical solvents and stabilizers, it is possible to design a green synthesis process that can reduce the toxicity of both the final product and the manufacturing process. ZnO NPs are produced by adding a zinc salt, such as zinc nitrate or zinc acetate, to the biological extract. ZnO NPs formation is also increased in many cases by addition of NaOH or a novel stabilizing agent like curcumin, sodium lignosulfonate, polyol etc. The mixture solution metal salt and biological extract gives a paste that is heated to obtain the ZnO powder [21]. Use of different biological substrates with varying compositions, the level of zinc salts, reaction duration, pH, and temperature greatly influence sizes and morphologies of particles. Chinnasamy et al. [22] studied the impact of many synthesis factors, including temperature, biological sample and zinc content and reaction time, on the size range and yield of created ZnO NPs. The reported conditions for highest yield were 65 g L<sup>-1</sup> zinc precursor, 200 °C temperature and the reaction time of 2 h. Among all the characteristics studied, the concentration of zinc nitrate influenced the particle size the most. Singh et al. [23] reported effects of quantity of plant extract and zinc precursor, reaction time, and incubation temperature on synthesis of ZnO NPs by using *Eclipta alba* leaves. The authors discovered that increasing the quantity of zinc acetate (1.0–5.0 mM) enhanced particle size uniformity. Furthermore, a strong relationship between *Eclipta alba* extract concentration and UV absorbance peak intensity led to improved ZnO NPs creation, which may have been caused by more antioxidants being available for use during synthesis as a result of the increased plant extract content. These phytochemicals are thought to be crucial in the creation of metal and metal oxide NPs generated through green synthesis [24]. Singh et al. [23] also investigated the influence of temperature ranging from 20 to 100 °C on the

generation and size of ZnO NPs. According to their findings, higher temperatures enhanced ZnO NPs production, but a short reaction response time during synthesis reduced particles growth rate and produced small size. There are several scientific studies that shows biological substrate are exclusive resources for the biosynthesis of NPs [25]. However, the complexities of biological substrates make it difficult to evaluate and characterize the chemical process that occurs during green synthesis.

### 2.1.1 Methods of Green Synthesis of Zinc Oxide Nanoparticles (ZnO NPs)

The efficiency of green synthesis of metallic NPs has been established in the laboratory only [26]. Thus, determining the mechanism path of green synthesis production is critical for large-scale process development. Hence, in this review, we discuss current achievements in the literature related to ZnO NP synthesis by utilizing various biological substrates.

**2.1.1.1 Bacteria** A microbial culture or biomass may be used to biosynthesize the metals and metals oxide NPs, it may occur either through an extracellular or intracellular environment [27]. Metals and metals oxide NPs production by microbial sources can occur either extracellularly or intracellularly. Numerous studies indicate that extracellular creation of NPs is a nitrate reductase-mediated synthesis where metal ions are transformed into metal NPs [28]. There are two way extracellular synthesis processes either by enzyme presents on the cell membrane or the releasing of these enzymes into the growth medium as an extracellular enzyme. A nitrogen cycle enzyme called nitrate reductase is responsible for catalyzing the transformation of nitrate into nitrite. For example, the electron transfer from NADH through NADH-dependent reductase, which acts as an electron carrier, initiates the bio-reduction of  $Zn^{2+}$ . As a result,  $Zn^{2+}$  received an electron and it reduced to  $Zn^0$ , that's leads to subsequent generation of ZnO NPs [29]. In case of the extracellular synthesis, different studies propose that the micro-organisms release various proteins and enzymes that can participate in reduction of metal ions to contribute for stability of particles. An enzyme produced by cells of bacteria (*Bacillus licheniformis*) that stabilized the ZnO NPs was investigated by Tripathi et al. [25]. They first formed  $Zn(OH)_2$  from the reaction mixture of zinc acetate and sodium bicarbonate and then that product was thermally treated to generate ZnO nuclei. The bacterial cell enzymes subsequently stabilized the ZnO NPs to prevent particle agglomeration. Furthermore, Selvarajan et al. [30] proposed the enzymes released by the micro-organism to be major factors for formation of ZnO NPs. The authors also suggested that pH of the reaction mixture and the electrokinetic potential of bacterial cells may participate in the

synthesis process by reduction of metal ions and as well as activating the biosynthesis of the NPs. A similar report on extracellular synthesis using *Staphylococcus aureus* was based on the same concept for the biosynthesis of ZnO NPs [27]. Another report for synthesis showed that the activated ammonia from ureolytic bacteria (*Serratia ureilytica*) seems to be driving force to produce ZnO NPs [31]. On the subject of intracellular synthesis, the cell walls of microorganisms and the charge of ions both play essential roles in the synthesis of NPs. This entails specific ion transit in the presence of enzymes, coenzymes, and other molecules in the microbial cell. Microbes have a variety of polysaccharides and proteins in their cell walls, which act as active sites for the binding of metal ions [32]. The route of formation can be very difficult because of complexity of processes and cell composition. According to many studies, cells take in metallic ions for reduction by proteins and enzymes to produce NPs [33]. For instance, different shapes of silver NPs obtained from *Pseudomonas stutzeri* recognized through Transmission electron spectroscopy (TEM) have given the idea about formation of particles within the cell of bacteria. A report identified formation of gold NPs with different sizes between 5 and 30 nm obtained from *Lactobacillus kimchicus* utilizing similar analyzing process [34]. When compared, intracellular synthesis of silver NPs is more complex to adjust with dispersion, morphology and sizes of the particles [35]. A similar and well known process is internalization of  $Zn^{+2}$  inside the micro-organism [36] and ZnO NPs biosynthesis through this intra-cellular mechanism could be plausible to rout to gain nanomaterials. Nevertheless, the reports suggest that extracellular mechanism is most familiar route to synthesis of ZnO NPs using different bacterial cultures [37] but also requiring some additional steps for obtaining NPs, which includes release of the particles from lysed microbial cells [38]. As a result, extracellular synthesis is a more time-consuming and costly process in which several extracellular enzymes directly reduce or chelate metal ions.

**2.1.1.2 Fungi** The use of fungal based samples for biosynthesis of metal oxide NPs follows the same mechanistic approach as detailed in the previous paragraph. For example, formation of ZnO NPs using *Aspergillus fumigates* cell culture was reported by Raliya et al. [39]. They proposed microorganism release the proteins and enzymes in control for the formation and encapsulation of NPs. *Aspergillus niger* cell-free filtrate was also used to form the extracellular ZnO NPs [40]. Due to higher concentration of metabolites present in fungi, these cells have higher potential to reduce the metal salt to nanomaterials when compared to bacterial culture synthesis [41].

**2.1.1.3 Plants** For green synthesis of NPs, Plants source are the most widespread biological substrates [42]. The real fact

is that vegetative part of plant are to be most reliable, easy to operate and less harmful when compared with micro-organism. For synthesis purposes, using plant-based substrates also eliminates any health hazards or safety problems associated with harmful bacteria. Also, plant extracts may be easily produced by simply extracting the plant metabolites in a solvent (typically ethanol or distilled water) [43]. The various part of plants such leaves, roots, seeds, and fruits have all been used in this way [44]. In the plants, active substances such methylxanthines, phenolic acids, flavonoids and saponins are present in a considerable amount [45, 46]. All of these phyto-chemical compounds act as antioxidants that may neutralize active oxygen species (AOS) and also act as chelating agents for different metals during synthesis of NPs [47]. These phyto-chemicals mediate production of metal-based NPs owing to their capacity to reduce or chelate metal ions apart from stabilization of the NPs formed [48]. Despite the understanding of phytochemical capabilities, plant extracts include a huge diversity of active chemicals in varying quantities [45]. This property makes it difficult to quantify the precise number of molecules taken from a plant. The exact mechanistic path of metal and metal oxide NPs production utilizing vegetative substrates is still a difficulty to be overcome. In published research theories, compounds extracted from a plant reduce a zinc salt or create complexes with it [44].

On the basis of the chemical properties of flavonoids, limonoids, and carotenoids, the author hypothesized a mechanistic pathway for synthesis of ZnO NPs. In this mechanistic work, phyto-chemicals formed coordinated complexes with  $Zn^{+2}$  ions and the same were thermally degraded to create zinc oxide with an average size of

9.7 nm [49]. The similar mechanism reported by Matinise et al. [24] where phytochemicals present in *Moringa oleifera* leaves chelated  $Zn^{+2}$  metal ions and then calcination done to produce the ZnO NPs. The hydroxyl ( $-OH$ ) stretching bands in both plant extract and ZnO NPs were associated in Fourier transform infrared (FTIR) analysis as a probable sign of the development of zinc complexes with antioxidants [50]. However, when *Eclipta alba* leaves are used to make ZnO NPs, the plant active chemicals converted  $Zn^{+2}$  ions to zinc metal instead of creating coordinate complexes. Following biological reduction, zinc metal combines with dissolved oxygen to generate ZnO nuclei and phyto-chemicals may also work as stabilizers, inhibiting particle aggregation [22]. Abdelmigid et al. [51] showed aqueous  $Zn^{+2}$  getting converted to ZnO NPs by extracts of pomegranate peel (PPE) and coffee ground (CGE). It was hypothesized that the activity of phytochemical compounds released into the reaction mixture would decrease  $Zn^{+2}$  to ZnO NPs with the help of their functional groups.

All above described research showed multiple sources for ZnO NPs synthesis to be simple, sustainable and cost effective approaches for synthesis. These plant-based ZnO NPs demonstrated an advantage over conventionally produced ZnO NPs, with this attribute definitely having an influence on piezoelectric nanomaterial research, pushing attention toward the use of these green methodologies rather than physicochemical procedures and various mode of synthesis of green NPs has been shown in Fig. 1. [52].

There are many biological sources of synthesis for ZnO NPs and their various modes of action that have so far been described in the literature and also presented in Table 1.

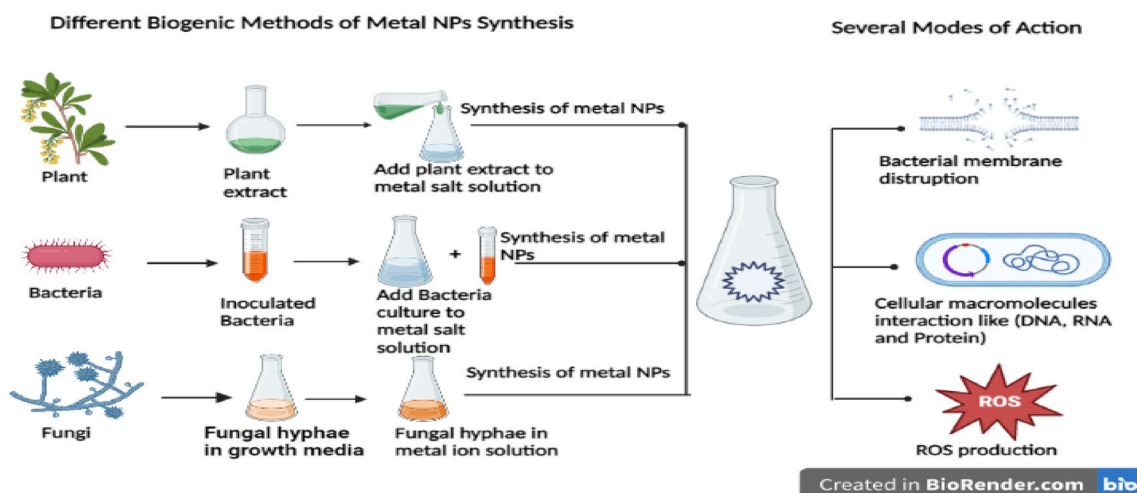


Fig. 1 Different biogenic methods of metal NPs synthesis



**Table 1** ZnO NP synthesis from several biological sources

Biological source	Zinc source	Average size (nm)	Shape	Reference
<b>Bacteria</b>				
<i>Lactococcus lactis</i>	Zn(NO <sub>3</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	55–60.5	Hexagonal	[53]
<i>Serratia nematodiphila</i>	ZnSO <sub>4</sub>	10–50	Uniformly spherical	[54]
<i>Bacillus licheniformis</i> Dahb1	Zn (CH <sub>3</sub> COO) <sub>2</sub>	10–100	Hexagonal	[55]
<i>Staphylococcus aureus</i>	Zn(O <sub>2</sub> CCH <sub>3</sub> ) <sub>2</sub>	10–50	Acicular	[27]
<i>Aeromonas hydrophila</i>	ZnO	57.72	Oval	[56]
<b>Plant</b>				
<i>Cassia fistula</i>	Zn(C <sub>2</sub> H <sub>3</sub> O <sub>2</sub> ) <sub>2</sub> ·2H <sub>2</sub> O	68.1	Spherical	[57]
<i>Parthenium hysterophorus</i>	Zn(NO <sub>3</sub> ) <sub>2</sub>	10	Spherical	[58]
<i>Eucalyptus globulus</i>	Zn (NO <sub>3</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	27–35	Spherical	[59]
<i>Brassica oleracea</i>	ZnCl <sub>2</sub> ·7H <sub>2</sub> O	14	Spherical	[60]
<b>Fungus</b>				
<i>Phanerochaete chrysosporium</i>	ZnSO <sub>4</sub> ·7H <sub>2</sub> O	50	Hexagonal	[61]
<i>Trichoderma harzianum</i>	Zn(C <sub>2</sub> H <sub>3</sub> O <sub>2</sub> ) <sub>2</sub> ·2H <sub>2</sub> O	8–23	Hexagonal	[62]
<i>Aspergillus niger</i>	ZnCl <sub>2</sub>	40	Hexagonal	[63]

### 3 Biomedical and Other Application of ZnO NPs

Nanotechnology's incorporation into medical research has opened up new opportunities and improved our knowledge of molecular biology. As a result, there is the possibility of developing innovative approaches for treating illnesses that were previously impossible to address owing to size constraints [64]. Bio-functional NPs production is significant for biomedical applications, and it has lately attracted the interest of a number of research groups working in various research fields [65]. At the present time, a variety of materials and chemical processes are undergoing research for clinical applications, as we indicated in this review with various medicinal uses of ZnO NPs. Zinc is a naturally occurring element that acts as a considerable role in the metabolism of humans, animals, and plants. Zinc oxide is also extensively utilized for cosmetic, pharmaceutical, and medicinal applications and is acknowledged as useful nutritional supplement [66].

#### 3.1 Antibacterial Uses of Plant-Based ZnO NPs

A wide range of illnesses due to bacterial infections, as well as the emergence of multidrug resistance, have necessitated development of new carriers for efficient drug delivery. Nanotechnology has emerged as a revolutionary strategy for fighting bacterial illnesses. Several different types of metal NPs act as anti-biotic agents [such as (ZnO), titanium oxide (TiO<sub>2</sub>), copper oxide (CuO) and iron oxide (FeO)] for successful action on disease causing bacteria [67]. The antibacterial properties of NPs are connected to inherent traits such as strong reactivity and a significant ratio of surface area to volume, which allow them to interact with more ligands on

the surface [68]. When paired with green synthesis methodologies, ZnO NPs have the most impressive impact of among all NPs. ZnO NPs are made from a range of natural source materials, including bacteria and plants, and have a strong anti-bacterial impact. Plant-mediated or phytochemical production of NPs have strong presence in published reports, owing to the large variety of raw materials available and the potential of creating synergetic nanostructures that combine the antibacterial capabilities of plant extract and NPs [69]. Suresh et al. [70] suggested an interesting approach for the synthesis of ZnO NPs based on the utilization of extract of *Cassia fistula* as source of reducing components like flavonoids (12.5%) and polyphenols (11%). These metabolites acted as capping agents to permit small sized ZnO NPs in range from 5 to 15 nm with hexagonal wurtzite shape. The scavenging activity of ZnO NPs was tested through 2,2-diphenylpicrylhydrazyl (DPPH) free radicals and outstanding anti-bacterial activity was also assessed towards *E. coli*, *S. aureus* and *Plasmodium desmolyticum*. In the same way, the biological synthesis of 60–70 nm ZnO NPs from zinc acetate was shown by employing *Trifolium pratense* flower extract as source of novel reducing and capping agents [71]. An antimicrobial effectiveness of this nanomaterial was shown against *S. aureus* and *P. aeruginosa* (clinical and standard strains), apart from standard strain of *E. coli*. This study also revealed stronger anti-bacterial activity of ZnO NPs than gentamicin against *Pseudomonas aeruginosa*. The extract of *Boerhavia diffusa* leaves in water was used to create 140 nm ZnO NPs with efficient stability. According to anti-bacterial and anti-biofilm capabilities examined, the antibacterial impact was shown to be substantial against Methicillin-resistant *S. aureus* (MRSA) strains [72]. In a separate study, *Artocarpus gomezianus* fruit extract was used to produce spherical ZnO NPs and also involved use of

an environmentally acceptable green combustion approach [73]. TEM investigations indicated that ZnO NPs produced with 10% fruit extract were extremely homogeneous, spherical in form, and loosely clustered, with diameters of 39, 35, and 31 nm for 5, 10, and 15 ml used volumes respectively. The zone of inhibition method was utilized to investigate the anti-bacterial impact, and it was discovered that the NPs displayed substantial antibacterial activity at concentrations ranging from 10 to 500  $\mu\text{g ml}^{-1}$  against *S. aureus*. Saravanan et al. [74] employed *Bacillus megaterium* extracts as novel source of reducing and capping agents to synthesize ZnO NPs with discrete shape and size from  $\text{Zn}(\text{NO}_3)_2$  as a metal source for NP synthesis. A Field emission scanning electron microscopy (FESEM) examination revealed primarily rod-like and cubical ZnO NPs with sizes from 45 to 95 nm. The multifaceted impact of the NPs on *H. pylori* was investigated, and bacterial growth was inhibited by 16–17  $\mu\text{g ml}^{-1}$  levels. The researchers discovered that ROS produced on the NPs' surface attach to the bacterial surface and use electrostatic forces to kill germs. Mechanical interaction between the bacteria and the ZnO rod surface was suggested to contribute to free  $\text{Zn}^{+2}$  ion antibacterial activity. ZnO NPs were also synthesized from exopolysaccharides (EPS) of probiotic Dahb1 strain of *Bacillus licheniformis* as novel and effective approach using EPS as reducing and stabilizing agent for co-precipitation method for synthesis of NPs [55].

This approach revealed a crystalline, hexagonal structure with sizes between 10 and 100 nm apart from SPR (surface plasmon resonance) centered at 375 nm. A significant proven concentration was 100  $\mu\text{g ml}^{-1}$  of ZnO NPs that inhibited efficient growth of numerous bacterial strains, for example *Proteus vulgaris*, *Bacillus subtilis* and *P. aeruginosa*. An interesting approach for antibacterial activity of ZnO NPs was exploited using *Penicillium chrysogenum* by Mahmoud et al. [75] ZnO NPs are effectively reduced by proteins released by fungal strains. In this case, the filtrate of *P. chrysogenum* was employed as bioreactor for the biogenic production of ZnO NPs by using biological active macromolecules like proteins and enzymes. This strain of fungus

*P. chrysogenum* was tested for activities against Gram-positive and Gram-negative bacteria i.e. *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Salmonella typhimurium*. The inhibitory effect of biosynthesized ZnO NPs might be due to NPs reacting with bacterial proteins by combining the thiol (-SH) group, resulting in protein inactivation and bacterial growth. The synthesis of ZnO NPs by the aqueous extracts of two fungal strains viz. *Fusarium keratoplasticum* (A1-3) and *Aspergillus niger* (G3-1) were employed. These two different fungal strains yielded different shapes of ZnO NPs i.e. hexagonal by *F. keratoplasticum* strain (A1-3) and nano-rod through *A. niger* strain (G3-1). The anti-bacterial activities of NPs were shape-dependent. When compared to hexagonal ZnO-NPs, nano-rod NPs demonstrated improved anti-bacterial and UV-protection activities against harmful microorganisms. So, there are different source mediated syntheses of ZnO NPs and their antibacterial modes of action on various target bacterial strains, as shown in Table 2.

### 3.1.1 Antibacterial Mechanism of Action of ZnO NPs

The action of NPs is not specific, so there is no single mechanistic approach for antibacterial activity and this complicates the understanding of the basic mechanism behind anti-bacterial action. The components of cell membrane like proteins interact chemically to hydrogen peroxide which is possible with aqueous suspension of ZnO. Therefore, there are various chemical components formed describing different ways of anti-microbial actions [83]. The main antimicrobial mechanisms which have been reported are (i) Reactive oxygen species (ROS) generation [84], (ii) the cellular integrity degraded after interaction of ZnO NPs to bacterial cell wall [85], and (iii) the liberation of  $\text{Zn}^{+2}$  ions and internalization to the bacterial cell [86]. The ROS generation by different metal oxides is one of the most widely documented mechanisms for anti-bacterial action in the literature. Some of ROS such as superoxide anions ( $\text{O}_2^-$ ), hydroxyl radicals ( $\text{HO}_2^-$ ), and hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), may damage

**Table 2** Different green sources for synthesis of ZnO NPs and their mode of action on various strains of bacteria

Platform	Raw material	Size (nm)	Target bacteria	Reference
Bacteria mediated	<i>Paraclostridium benzoelyticum</i> strain 5610	48.22	<i>H. felis</i> , <i>H. salomonis</i> , <i>H. suis</i> , and <i>H. bizzozeronii</i>	[76]
	<i>Lactobacillus plantarum</i> TA4 cell-biomass and supernatant	291.1, 191.8	<i>E. coli</i> , <i>Salmonella</i> sp. <i>S. aureus</i> , <i>S. epidermidis</i>	[77]
Plant mediated	<i>Musa paradisiacal</i> peel extract	20	<i>S. enterica</i> , <i>K. pneumoniae</i> , <i>B. cereus</i> and <i>S. aureus</i>	[78]
	<i>Rubus fairholmianus</i> root extract	11.34	<i>S. aureus</i>	[79]
	<i>Myristica fragrans</i> fruit extract	41.23	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. Aeruginosa</i> and <i>S. aureus</i>	[80]
	<i>Lippia adoensis</i> leaf extract	19.78	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. aureus</i> , and <i>E. faecalis</i>	[81]
Fungi mediated	<i>Phanerochaete chrysosporium</i>	50	<i>S. aureus</i> and <i>E. coli</i> ,	[61]
	<i>Xylaria acuta</i>	34–55	<i>S. aureus</i> <i>B. cereus</i> , <i>P. aeruginosa</i> and <i>E. coli</i>	[82]

biological components including DNA, proteins, and lipids [87]. The similar charges present on both bacterial cell wall and two species radicals such as hydroxyl radicals and super oxides make entry of these two species into bacterial cell wall difficult, but ROS may still inflict harm in close proximity [88]. Bacteria more susceptible to  $H_2O_2$  seem to be more sensitive to ZnO NPs also [89], so hydrogen peroxide was proposed to be the mechanism behind ZnO NPs antibacterial action. There are different mechanisms that can destroy the bacterial cell by releasing ions of  $Zn^{2+}$ . The dispersion of ZnO NPs in solution in the form of ions adds to their antibacterial activity by disturbing the enzymatic system and lowering amino acid metabolism [36]. Cho et al. [90] performed tests on rats based on this dissolution and found that ZnO NPs stay intact at biological pH. ZnO NPs can easily dissolve in acidic medium (pH 4.5) as in bacterial lysosomes and cause death due to attachment of these  $Zn^{2+}$  to the various bio-molecules present inside the different bacterial cells. Li et al. [91] assessed the anti-bacterial activity of ZnO NPs suspensions based on ROS generation and  $Zn^{2+}$  ions release. There was no suppression of *E. coli* at a  $Zn^{2+}$  concentration of roughly  $1\text{ mg l}^{-1}$ , according to the researchers. The growth rate of *E. coli* reduced as ROS level increased, it was indicating that the released  $Zn^{2+}$  ions had a lower impact. In addition, Baek et al. [92] reported the free ions' release by several NPs including ZnO NPs by using strains of *E. coli*, *S. aureus* and *B. subtilis*. The release of  $6.8\text{ mg m}^{-1}$   $Zn^{2+}$  ions was reported from  $125\text{ mg ml}^{-1}$  of ZnO NPs and resultant anti-bacterial activity was assessed due to bacterial contact with these ions. The findings revealed minimal effect of free ion activity (ranging from 2 to 3% for all strains tested) but considerable toxicity of ZnO NPs for all strains examined.

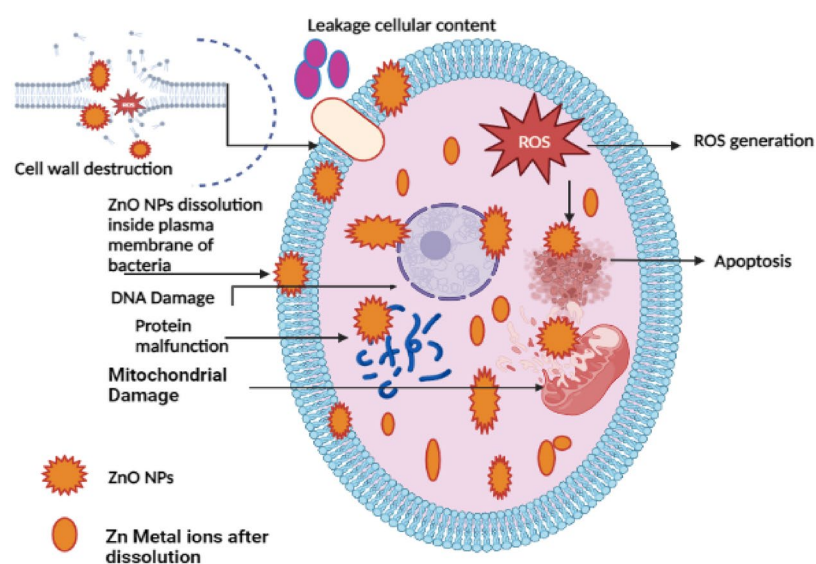
So, the link of NP activity with intrinsic metal particle toxicity was hypothesized [92]. One more potential toxicity mechanism for ZnO NPs is towards the cell wall, causing bacterial integrity to be compromised [93]. The toxicological effects of ZnO NPs on *E. coli* were studied by Brayner et al. [85] and findings revealed that the bacterium cells were injured, resulting in membrane disorganization and increased membrane permeability, resulting in the buildup of ZnO NPs in the cell membrane as well as NP internalization. ZnO NPs toxicity is not necessarily determined by their internalization in the bacterial cell, as previously stated. By producing ROS or becoming more soluble, ZnO NPs can change the environment around bacteria. This releases  $Zn^{2+}$  ions, which are more mobile and have a stronger attraction to the biomolecules inside of bacteria because they have a positive charge whereas the biomolecules have a negative charge.

Both of which can lead to cellular harms which include of cellular membrane disintegration, genetic material impairment, protein malfunction and mitochondrial damage that leads towards cell death [94]. There are different toxicity pathways of ZnO NPs towards the bacterial cells and that is eventually affects the growth and development of cells and which has been outlined in Fig. 2 [95].

### 3.2 ZnO NPs as Potent Antioxidant Agents

Zinc is an essential mineral that helps with antioxidant protection, growth, and immune system function [96]. ZnO NPs have been shown to display strong antioxidant effects inside cells as well as in cell-free environments. Das et al. [97] used DPPH free radical scavenging to assess the time and concentration-dependent antioxidant scavenging capacity of

**Fig. 2** Mechanism action of ZnO NPs as an anti-bacterial agent



ZnO NPs (40–50 nm & spherical). This study discovered substantial antioxidant activity of ZnO NPs due to oxygen to nitrogen electron density transfer for holding odd electrons in the DPPH molecule. Ebrahimiasl et al. [98] investigated polypyrrole/zinc oxide/chitosan bio-nano composite with size range between 100 and 1000 nm and spherical shapes. This material showed a high DPPH scavenging activity with the increased concentration of ZnO composite [99, 100]. The antioxidant properties of biosynthesized 27–54 nm, spherical ZnO NPs were investigated by Rehana et al. [101] using extracts from *Azadirachta indica*, *Moringa oleifera*, *Hibiscus rosa-sinensis*, *Ceropegia candelabrum*, and *Tamarindus indica*. Several different anti-oxidant scavenging activities (i.e. against DPPH, hydroxyl radicals, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS<sup>+</sup>), superoxide and hydrogen peroxide) were efficiently performed by these biosynthesized ZnO NPs. Furthermore, in vivo antioxidant activity of ZnO NPs was checked in broiler chickens by Hafez et al. [102] who prepared spherical shaped, 39.2 nm ZnO NPs that acted as dietary supplementation at the concentrations of 40 and 80 ppm and considerably improved the action of antioxidant enzymes superoxide dismutase (SOD) and catalase apart from lowering the level of Malondialdehyde (MDA).

The leaves extract of *Azadirachta indica* was used to biosynthesize ZnO NPs within the range of 20 nm and non-spherical in shape by Sohail et al. [103]. The produced ZnO NPs demonstrated effective DPPH radical scavenging and ferric reduction antioxidant activities (FRAP). Although a few studies have revealed that ZnO NPs have intracellular antioxidant activity through activating antioxidant enzymes, the direct ROS scavenging ability of ZnO NPs in intracellular conditions has yet to be validated. The antioxidant activities of various green ZnO NPs are represented in Table 3.

### 3.3 Anti-cancerous Application of ZnO NPs

Zinc is a necessary mineral that regulates enzyme activity to keep the body in a state of homeostasis, while a lack of it can trigger and encourage the growth of malignant cells [110]. The tumor suppressor gene p53, which controls apoptosis by activating the caspase-6 enzyme, is highly dependent on

zinc to be active [111]. Additionally, ZnO NPs have a special electrostatic property that makes it easier to target cancer cells specifically. As a result of the high quantity of anionic phospholipids seen on the surface of cancer cells, ZnO NPs are attracted to them electrostatically. The tiny size of ZnO NPs facilitates the penetration and retention of NPs inside the tumor cells for further action [112]. This boosts cellular uptake of ZnO NPs by the cancer cells and ultimately results in cytotoxicity [113]. ZnO NPs create a huge quantity of ROS in cancer cells as compared to normal cells, resulting in a substantial degree of oxidative stress leading to death of these cells and these anti-cancerous action has been describe in Fig. 3 [114].

ZnO NPs induced apoptosis in leukemic cells while having no harmful effects on counterpart cells [115]. ZnO NPs have also been shown to induce considerable selective toxicity against tumor T cells while causing minimal damage to normal body cells [116]. It had been shown that the cytotoxic action of ZnO NPs on brain tumour cells is selective, with no evidence of damage in normal human astrocytes [117]. Murali et al. [118] examined the anticancer potential of ZnO NPs prepared from extract of *Mangifera indica* leaf against the lung cancer cell line (A549) and found that prepared ZnO NPs were efficient anticancer agents with cytotoxic effects similar to those of low doses of cyclophosphamide.

The effectiveness of biosynthesized ZnO NPs as an anti-cancer agent was dose-dependent, indicating that the anti-cancer activity of ZnO NPs was at its peak when greater doses were supplied. Drug delivery based on the usage of ZnO NPs might decrease the amount of medications needed for therapy and eliminate other adverse effects by targeting the precise locations of cancer cells [119]. ZnO NPs biodegradability and low toxicity have enhanced their use in cancer treatment delivery when compared to other NPs.

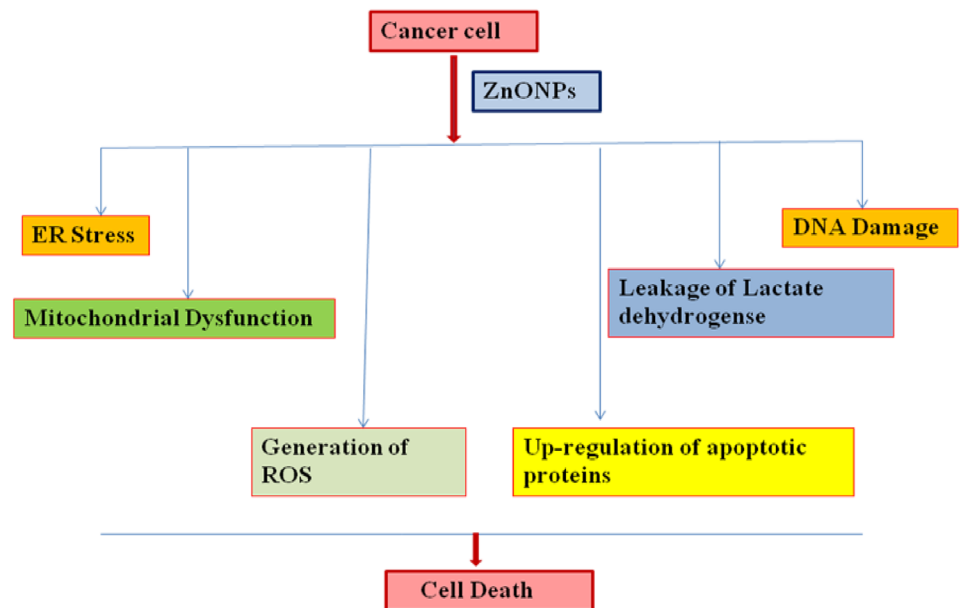
When medications like doxorubicin and paclitaxel were delivered on ZnO NPs, their solubility and toxicity improved [120]. Recently, the phyto-synthesis of ZnO NPs utilizing *Vinca rosea* leaves extract was carried out and investigated for anticancer effects on MCF-7 (breast cancer) cell line. ZnO NPs (81.75  $\mu\text{g ml}^{-1}$ ) had a robust cytotoxic impact against the MCF7 cell line. It has been proposed as an attractive possibility for the safe and successful treatment

**Table 3** Antioxidant applications of ZnO NPs

Species	Material	ZnO NPs average size (nm)/shape	Method/findings	Reference
<i>Malva neglecta</i>	Leaf, seed	40–50, Spherical	DPPH IC <sub>50</sub> = 250 $\mu\text{g/ml}$	[104]
<i>Tecoma castanifolia</i>	Leaves	70–75, Spherical	DPPH IC <sub>50</sub> = 100 $\mu\text{g/ml}$	[105]
<i>Scutellaria baicalensis</i>	Root	33.14–99.03, Spherical	DPPH IC <sub>50</sub> = 500 $\mu\text{g/ml}$	[106]
<i>Luffa acutangula</i>	Peel	> 100, Spherical and Cuboid	DPPH IC <sub>50</sub> = 134.12 $\mu\text{g/m}$	[107]
<i>Coccinia abyssinica</i>	Tuber	10.4, Hexagonal	DPPH IC <sub>50</sub> = 127.74 $\mu\text{g/mL}$	[108]
<i>Ruta graveolens</i>	Stem	28, Spherical	DPPH IC <sub>50</sub> = 9.34 $\text{mg/ml}$	[109]



**Fig. 3** Various possible processes of ZnO NPs triggered the cytotoxicity of cancerous cells



of cancer to utilize NPs in targeted medication delivery and possible processes of ZnO NPs induced cancer cell lines cytotoxicity [121]. Table 4 summarizes the different plant derive ZnO NPs, it shows the cell cytotoxicity.

### 3.4 Antidiabetic Activities of ZnO NPs

A chronic metabolic condition is the Diabetes mellitus (DM) that affects people all over the world. According to current reports, the number of cases is predictable to go up to 578 million by 2030 and even 700 million by 2045 from the predicted 463 million cases in 2019. A hallmark of diabetes is hyperglycemia, which is typically brought on by a decline in the amount of insulin in the blood [129]. As a result, several low-cost medications are desperately needed. Zinc, for example, is required for glucose metabolism and homeostasis, and zinc deficiency has been associated to diabetes. Zinc is also recognized to be important for insulin production, storage, and secretion [130]. In rats, Umrani et al. [131] investigated the anti-diabetic effects of 80–100 nm ZnO NPs and zinc sulphate salt. They found greater impact of 1, 3,

or 10 mg kg<sup>-1</sup> ZnO NPs (for 56 days) on diabetic rats as compared to 30 mg kg<sup>-1</sup> ZnSO<sub>4</sub>. It also improved glucose uptake in adipocytes apart from insulin activity in skeletal muscle and liver cells. The antibiotic streptozotocin (STZ), which causes the loss of pancreatic islet cells, is frequently employed experimentally to create a model of type 1 diabetes mellitus (T1DM) [132].

In order to feed STZ-induced diabetic rats orally for 30 days at a dose of 10 mg kg<sup>-1</sup>, Hussein et al. created pullulan-based ZnO NPs (100 nm and virtually spherical) [133]. In diabetic rats, ZnO NPs generated a considerable decrease in blood glucose with increase in insulin concentration. Other effects were reduction in insulin resistance by boosting level of phosphatidylinositol 3-kinase (PI3K) and providing antioxidant protection by enhancing SOD (Super-oxide dismutase) and plasma paraoxonase activity in RBCs. Furthermore, ZnO NPs induced an increase in some omega-6 fatty acid levels (alpha-linolenic acid and decosahexaenoic acid) and a decrease in other omega-6 fatty acid levels (arachidonic acid, linoleic acid, and Oleic acid) in the cell membrane. In type 2 diabetic rats, ZnO

**Table 4** Anticancer properties of ZnO NPs

Plant	Raw material	Size	Target cell line	Refs.
<i>Solanum nigrum</i>	Leaves	30.8 and 86.8 nm	HeLa cells	[122]
<i>Salvadora persica</i>	Bark	35–45 nm	Brain glioblastoma cells	[123]
<i>Raphanus sativus</i> var. <i>Longipinnatus</i>	Leaves	5–5 μm	Lung cancer cell line (A549)	[124]
<i>Crotalaria verrucosa</i>	Leaves	16–38 nm	HeLa and DU145 cell lines	[125]
<i>Leucaena leucocephala</i>	Leaves	50–200 nm	Dalton lymphoma ascites (DLA) cells	[126]
<i>Mangifera indica</i>	Leaves	47.7 nm	Lung cancer cell line (A549)	[127]
<i>Eclipta prostrata</i>	Leaves	20–75 nm	Hep-G2 cell line	[128]

NPs (40 nm) were administered orally for 28 days at a dose of 10 mg kg<sup>-1</sup> to examine the positive effects of ZnO NPs [134]. ZnO NPs therapy decreased blood glucose levels in diabetic rats while raising pancreatic interleukin-10 (IL-10) and blood insulin. Additionally, ZnO NPs decreased pancreatic damage brought on by oxidative stress by regenerating the pancreatic antioxidant defense system and overall antioxidant capacity (TAC).

In rat models of alloxan-induced diabetes, Bayrami et al. [135] prepared ZnO NPs (19 nm & spherical) from extract of *Urtica dioica* leaf and compared their antidiabetic effects with chemically synthesized ZnO NPs. The diabetic rats were given either ZnO NPs at 10 mg dl<sup>-1</sup> or ZnO-extract at 8 mg dl<sup>-1</sup> intraperitoneally for 16 days. When compared to chemically synthesized ZnO NPs, green produced ZnO NPs had better antidiabetic impact through raising insulin levels. As a result of the synergistic interactions between ZnO and *Urtica dioica* leaf extract, total cholesterol and triglyceride levels were decreased while high-density lipoprotein cholesterol (HDLc) was increased in diabetic rats. Table 5 explains the enhanced influence of ZnO NPs in experimental animals. The following facts are the basis of antidiabetic mechanisms of ZnO NPs: (a) In pancreatic beta-cells, ZnO NPs boost insulin release and improve the antioxidant defense system; (b) ZnO NPs help to increase glucose tolerance and lower glucose levels of blood. (c) ZnO NPs increase insulin sensitivity and absorption by the liver; adipose tissue and skeletal muscle; (d) ZnO NPs suppress gluconeogenesis in hepatocytes and lipolysis in adipocytes [136]. These above-described various modes of action of antidiabetic activity of ZnO NPs are shown in Fig. 4.

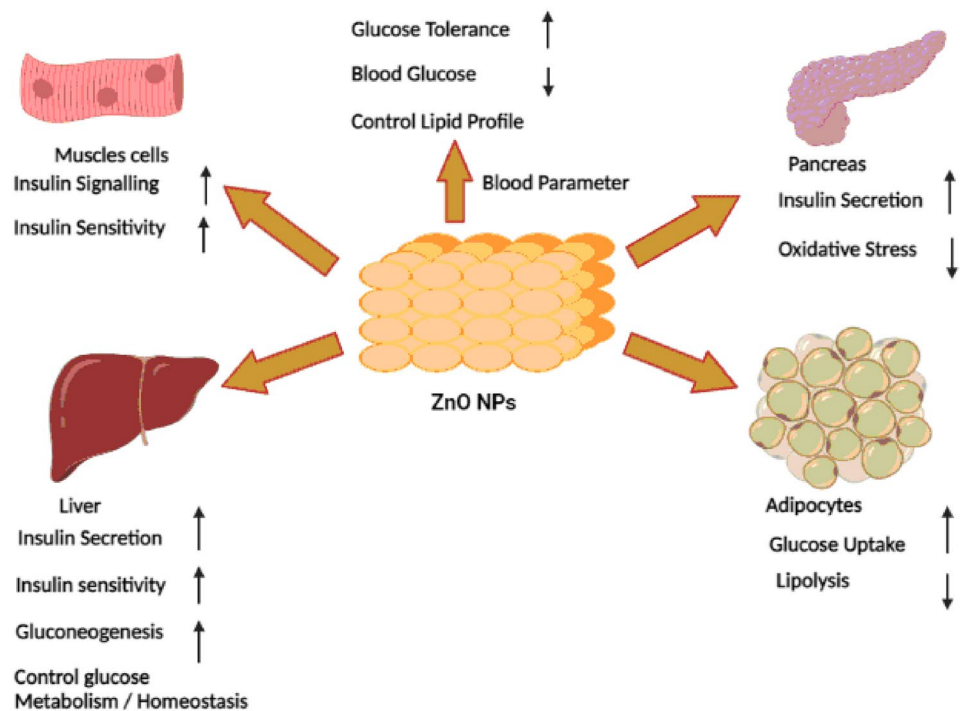
### 3.5 A New Prospective of ZnO NPs as an Antiviral Drug for SARS-CoV-2

In recent history, the globe has experienced several viral pandemics that have resulted in massive morbidity and mortality [142]. Viruses cannot reproduce on their own; they must first attach or cling to a living host cell, then replicate into more virions [143]. The ongoing COVID-19 widespread disease, caused by the acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), has emerged as universal socioeconomic liability, especially on public and individual medical protection systems due to significant morbidity, mortality, and economic disturbance [144]. SARS-CoV-2 infection was confirmed in 176,703,325 (about 2.3% of world population), with over 3,824,115 deaths worldwide by the middle of June, 2021 [Center for Systems Science and Engineering (CSSE 2021)] [145]. SARS-CoV-2 is an RNA virus with genome as single strand positive-strand RNA bigger than all other RNA viruses, while virus particle also has four structural and 16 non-structural proteins (nsp) [146]. COVID-19, the disease caused by SARS-CoV-2, predominantly affects birds and mammals upper respiratory tracts. Cough, fever, and breathing difficulties are the most serious clinical symptoms of COVID-19 [147]. Many scientists have worked hard to produce viable vaccinations and antiviral drugs to combat SARS-CoV-2. One strategy is to repurpose existing broad-spectrum antiviral medicines for covid-19 treatments. Favipiravir, remdesvir, hydroxychloroquine, and lopinavir, for example, have been shown to inhibit SARS-CoV-2 at micromolar doses, depending on the in vitro experiment [148]. However, nanomaterials represent a possible mode of dealing with SARS-CoV-2. Reina et al. [149] showed that virus-NP interaction can facilitate early viral entrance blocking, capsid protein oxidation, cell surface mimicry, and virus rupturing. Metallic NPs may bind

**Table 5** Enhanced influence of ZnO NPs in experimental animals

Animal	Concentration	Duration	Effect	Refs.
Albino Wistar	50 mg/kg	4 Months	In diabetic rats treated with ZnO NPs or glibenclamide (standard drug), glycated haemoglobin (HbA1c) levels were considerably lowered. However, in diabetic rats, ZnO NPs had an impact that was noticeably greater than glibenclamide's	[137]
Zebrafish embryos	100 mg/Kg	24 h	In hyperglycemic induced zebra-fish, ZnO NPs play an important function in decreasing blood glucose levels	[138]
Male Wistar rats	70 mg/kg	16 days	Compared to chemically produced ZnO NPs, green generated ZnO NPs have greater antidiabetic efficacy	[135]
Old male Wistar rats	10–100 mg/kg	6 h	In diabetic and healthy rats, ZnO NPs produce hyperglycemia after a short period of dosing	[139]
Male albino mice	120 mg/kg	28 days	Oxidative stress indicators and ROS levels were dramatically reduced, showing that ZnO NPs inhibited ROS production. Secondary hyper-glycemic complications	[140]
Male Wistar rats	10 mg/Kg	1 month	The protective impact of ZnO NPs against testicular diabetic complications	[141]
Male albino rat	10 mg/Kg	30 days	ZnO NPs show antioxidant action, anti-diabetic activity, and lower insulin resistance via raising PI3K levels and cell membrane omega-3 fatty acids	[133]

**Fig. 4** Modes of action of ZnO NPs as anti-diabetic agents



to virus surface glycoproteins, preventing viral attachment and entry into host cells [150]. Metallic NPs may also have antiviral properties by interfering with viral genetic materials [151].

An essential micronutrient is Zn, that is required for synthesis of proteins, nucleic acids, and neurogenesis and so is found in all tissues of the body. Zn is classified as a safe FDA-approved metal [152]. It has direct and virus-specific effects in the context of antiviral therapy, particularly with regard to respiratory viruses, and it increases potential antiviral immunity and resistance [153]. In vitro condition, Zn has been shown to inhibit both the SARS-CoV-2 and retrovirus RNA polymerase activity, as well as zinc ionophores, which obstructing the virus replication in cell culture [154]. Zn was also discovered to prevent the replication of various RNA viruses, including the respiratory syncytial virus, influenza virus, and several picornaviruses [155]. NPs are well known for having superior benefits such increased potency at low concentrations, increased efficacy against virus infections that are resistant to drugs, cost effectiveness, and availability for surface modification [156]. The antiviral modes of action for metal NPs were described in a study published in October 2020 [157]. SARS-CoV-2 is endocytosed before fusing with the cell membrane to release its DNA into the host cell. The interaction between the protein viral spike (S) and the angiotensin-converting enzyme 2 (ACE2) receptor causes viral cellular internalization [158]. Various enzymes, including TMPRSS2 (trans-membrane serine protease 2), catalyze the proteolysis of the CoV S proteins, which is required for the stimulation of cell to cell fusion [159].

The SARS-CoV-2 virus will then disassemble, releasing the nucleocapsid and viral DNA. Some of nonstructural protein like (3CLpro, nsp5 and PLpro, nsp3) enzymes are also involved in the splitting of these proteins to generate 16 nsp2-replication yields, which are necessary for the development of transcription complex [160]. Additionally, RNA-dependent RNA polymerase (RdRp), which facilitates the transcription and replication of the viral RNA genome during infection, plays a critical role in the SARS-CoV-2 life cycle. Metal NPs antiviral modes of action includes competition at cell-binding sites, host penetration prevention, destruction of virus particles prior to cellular entry, interaction with the viral genome, and, last but not least, exchange with replication factors are all part of it [161, 162]. ZnO NPs have been shown to interfere with the virus DNA polymerase function, hence preventing viral multiplication [163]. In contrast, ZnO NPs superiority and improved effectiveness over other antiviral metal oxide NPs, such silver and gold, are well documented and originate from their strong compatibility with biological systems, low cost, high safety, and stability [152]. Its inertness with a vast array of medications has also been noted [164]. At very low concentrations, zinc ions can inhibit ACE2 ability to metabolize substrates through a dose-dependent response (10  $\mu\text{M}$ ) [165]. It is also demonstrating that  $\text{Zn}^{2+}$  may be able to stop the interaction between the ACE2 and the SARS-CoV-2 spike protein [166]. Human plasma zinc concentrations typically vary from 10 to 18  $\mu\text{M}$  [167], and this concentration of zinc does not go over the physiological level. This evidence leads us to conclude that metal oxide nanoparticles (ZnO, iron oxides,

TiO<sub>2</sub>, etc.) primarily function by releasing cations into solution [168]. Additionally, the stable visible fluorescence of ZnO can be used in bio-imaging and drug delivery, as well as monitoring the internalization of drugs. All of the basic assumptions of the ZnO NPs provide the possibility to construct nanomedical viral-targeting therapeutics [169]. The possible mode of action of ZnO NPs as an antiviral therapy for SARS-CoV-2 has been shown in the Fig. 5.

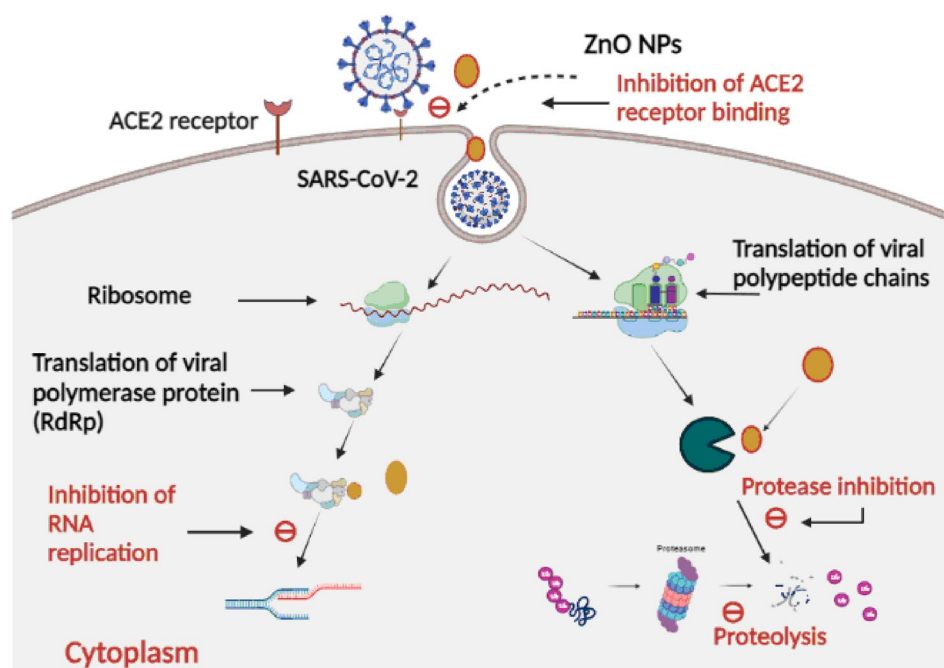
ZnO NPs have shown consistent antiviral efficacy against a wide range of viruses, while Zn itself has antiviral potential. It can trigger ROS, resulting in oxidative damage and viral death over times [170]. Zinc has antiviral characteristics make it potentially effective against SARS-CoV-2. It has been suggested that adding zinc to a diet may increase the effectiveness of other treatments [171]. ZnO NPs prevented the rate of the herpes simplex virus by 92% and brought down virus titer [172]. By electrostatic interference of NPs with the virus instead of hydrophobic interaction, a charged surface of ZnO NPs could affect virus infection ability by counteracting the virus rather than hinder with cellular targets [173]. Ghaffari et al. [174] showed that Zn<sup>2+</sup> ions can inhibit viral reproduction by increasing intracellular Zn<sup>2+</sup> concentrations, which can effectively reduce the replication of a variety of RNA viruses.

Plant derived NPs could be utilized to transport medications to the respiratory system in order to disrupt the interaction of ACE2 receptors and viral S protein. In that respect of developing a vaccine for SARS-CoV-2 or containing the cytokine storm, respectively, “nano-immunity by design” can assist us in designing matter for immunological regulation, either boosting or dampening the immune response.

With the potential to promote the growth of simple, quick, and affordable nanotechnology depended assays to examine the presence of SARS-CoV-2 and associated biomarkers, nanotechnology plays crucial roles in diagnostics [175]. A number of Ayurvedic Bhasma treatments are reported to be effective for treating COVID-19 because the formulations contain NPs, which have improved bioavailability and absorption when taken orally and sublingually [176]. Since cytokine release that cause harm and exacerbation are frequent in COVID-19 instances, anti-inflammatory medications are useful for treating the disease. As a result, anti-inflammation medicines are effective against COVID-19. Many Bhasma remedies have anti-inflammatory qualities; therefore, it can be assumed that Rajata Bhasma (Silver nanoparticles), Yashada Bhasma (Zinc nanoparticles), and Tamra Bhasma (Copper nanoparticles) will be useful in fighting with COVID-19 [177]. According to the World Health Organization (WHO), patients with COVID-19 infection had higher levels of plasma cytokines, interferons alpha (IFN), interferons gamma (IFN), and tumour necrosis factor-alpha (TNF). These plasma indicators can be used to assess the efficacy of these nanomedicines before and after treatment. Yashada Bhasma has the potential to be a novel antiviral drug against SARS-CoV-2 due to its anti-inflammatory, immunomodulatory, antiviral, and adjuvant properties [178].

Immunity derived from NPs can aid in the development of immune-modulators, also boosting or inhibiting the immune-reaction, which could be useful in the development of a vaccine for SARS-CoV-2 or in the prevention of cytokine storms [179].

**Fig. 5** The possible mode of action of ZnO NPs as an antiviral therapy for SARS-CoV-2





There is an alternate source that works as a disinfectant that has recently been synthesized from ZnO NPs for eliminating the developing SARS-CoV-2. This kind of disinfectant is called Nano-spray and it has been tested using 10% DMSO and distilled water for checking the antiviral efficacy in opposition to covid-19 by using different assay such as cytotoxicity and inhibitory concentration. ZnO NPs can produce many free radicals that can cause oxidative stress to SARS-CoV-2 and cause significant damage to the virus cellular membranes. These free radicals exhibited substantial antiviral action against SARS-CoV-2 at extremely low concentrations ( $IC_{50} = 526 \text{ ng ml}^{-1}$ ). It is a crucial accomplishment in the battle against SARS-CoV-2 [180].

## 4 Conclusion

Numerous scientific disciplines have greatly improved as a result of the development of nanotechnology, particularly in the area of materials used in biomedicine. Metallic and metal-oxide NPs have been utilized as drugs to treat conditions including cancer and bacterial infections as well as to identify vital biomarkers, the measurement of which may aid in accurate medical diagnosis. The creation of these beneficial NPs does have some negative effects on the environment and society, but development is not without its costs. The effectiveness of these materials in biomedicine is eventually impacted by this. With the novel concept of using organisms and biomolecules as specific reducing and capping agents for the development of NPs, green nanotechnology strongly asserts itself as a viable solution to prevent the production of harmful by-products and undesirable interactions with various biological membranes. In comparison to their conventionally manufactured counterparts, these green-synthesized nanostructures have been effectively used as biological agents and provide significant performance enhancement. These improvements include improved cyto-compatibility and clearance from the organisms as well as a moderate synthesis technique that is both affordable and ecologically responsible. ZnO has received extensive research as a useful nano-material for biomedicine applications. It has fruitfully complied with nano-science approaches and generated a synergistic impact, wherein the raw material properties and the properties of ZnO itself have led to strong antibacterial features, anticancer properties, and antiviral abilities.

Despite the examples in this paper, using biogenic ZnO NPs may have certain drawbacks. For example, the variety of the nano-materials is intrinsic to the synthetic protocols, where the raw materials may not be uniform in constitution and chemical distribution. Furthermore, the possibility of harmful components from bacterial or fungal cells attaching to the final NPs may be additional source of limitation for their medicinal usage. As a result, while some research

addressing the use of synthesized ZnO NPs as biomedical agents, there is still a lack of comprehensive understanding of their selective cytotoxic mechanism and appropriate bio-compatible procedures.

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## Declarations

**Competing interests** The authors declare no competing interests.

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