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A Review on Biofabrication of Zinc Nanoparticles, Its Mechanism and Recent Applications

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ABSTRACT

The field of nanotechnology has been one of the major focuses of research for scientists across the world which deals with the production and utilization of nanoscale materials. The increase in popularity of nanotechnology is due to its unique properties which are not present in bulk materials. In these recent years, zinc nanoparticles (Zn NPs) emerged as an important ceramic material that can be utilized across various fields such as medicine, food, textiles, wastewater treatment and many others. The fabrication of Zn NPs can proceed through three major pathways which are physical, chemical and green synthesis. As green synthesis is more environmentally friendly among these methods it is more preferred. Although many reviews on ZnNPs have been published but all of them either focuses on the mechanism, Biosynthesis or its application thus in this review, we summarized various techniques of green synthesis used in fabrication of Zn NPs, its mechanism and its recent applications in various fields reported in past few years.

Keywords: Zinc Nanoparticles, Green Synthesis, Biofabrication, Drug Delivery, Biosensors, Bio Imaging

INTRODUCTION

Nanotechnology has attracted immense interest during the last few decades the rapid growth of nano-technology, eco-efficiency, sustainability, and green chemistry are guiding the considerable interest and attention in the development of a variety of materials, products, and applications. In 1959, Richard Feynman introduced nanotechnology into the field of science and since then, it has spread to a wide range of applications such as electronic, optical, or magnetic device, medicine, energy, agriculture, and others [1]. Nanotechnology can be defined as technology that manipulates materials at a nanometer range (1-100 nm). Due to their size, nanomaterials exhibit unique physicochemical properties which make them favourable to be applied across various fields [2]. In nanomaterials production, there are two main approaches which are the top-down and bottom-up approaches (Fig. 1). In the top-down approach, bulk materials are broken down into nanoscale materials via various techniques while the bottom-up approach involves the building of nanomaterials through the joining of atoms [3]. The bottom-up approach is preferable as the resulted nanomaterials have lesser defects and homogeneous chemical compositions and this approach relies on chemical and green methods of production [3][4]. Between these two methods, chemical synthesis is considered unfavourable due to the high cost and usage of toxic chemicals which may lead to environmental pollution. Furthermore, a previous study shows that chemically synthesized nanomaterials interfered in biomedical applications due to their toxicity [5]. Therefore, a method that can overcome problems posed by the chemical method is needed and green synthesis emerged as the solution. In these recent years, due to the low cost and eco-friendly of green synthesis, researches regarding the production of nanomaterials have been focused on this method. Green synthesis which also commonly known as biological synthesis can be defined as a process that uses biomaterials such as plants and their extract, microorganism, and biopolymer to produce the target nanomaterials [3][6]. In green synthesis, the biomaterials can serve as either capping or stabilizing agents thus no additional reagents are needed [7]. Besides its low-cost and environmentally friendly, green synthesized nanomaterials have similar physicochemical properties to those chemically synthesized [6].

The three main biomaterials used in green synthesis have their own advantages and disadvantages. For plant extract, the synthesis process is simple and economical but polydisperse nanomaterials are generated. This is due to various phytochemicals present in the extract. Utilizing microorganisms in nanomaterials production can overcome nanomaterials polydispersity. However, the growth of microorganisms must be in controlled and sterile conditions which are relatively complex. Production of nanomaterials using biopolymers is relatively easy but some biopolymers are insoluble in water which makes them difficult to handle [7] [8]. There are many different types of nanomaterials classification with the most common being metallic, such as Ag, Au, Pt, Zn, and Cd, and metal oxide, such as ZnO, TiO_2, ZrO_2, and CeO_2, nanomaterials. Among them, metal oxides, especially Zn, have been widely investigated due to their unique size and shape-dependent properties [9]. It was reported that Zn has been used in ointments for skin treatment since at least two millennia B.C, in ancient Egypt and Rome. Today, Zn is currently being used across different industries such as rubber, ceramics, concrete manufacturing, cosmetics, food, and others [10]. With the rise of technology, the development of micro-and nanosized Zn is feasible and this can further broaden its applications. Zn is a semiconductor material with a wide bandgap width (3.37 ev) and large excitation binding energy (60 meV) [11]. It has strong pyroelectric and piezoelectric characteristics [12]. It has three crystal forms which are hexagonal wurtzite, cubic zinc blend, and rock salt. Among the crystal structures, wurtzite is the most stable and the other two only occur in special conditions [13]. Zn can also exist in many different nanostructures such as nanospheres, nanoplates, nanorods, nanotubes, nanoneedles, nanoribbons, nanobelts, nanosheets, nanoflowers, and many more [14]. These various structures of Zn can be produced through different synthesis methods. US Food and Drug Administration has considered Zn materials to be GRAS (generally recognized as safe) thus it is frequently used in food packaging as an antimicrobial agent [14]. Due to the high interest in green synthesis, the production of Zn nanoparticles (ZnNPs) in these recent years has been shifted towards this method. Nanomaterials technology and development have successfully served progress in various scientific areas. Because of its biocompatibility, special physicochemical characteristics, and cost-effective mass production, zinc based nanocomposites have been the most viable techniques for biological applications. Among the most important accomplishments is the advancement of vaccines against different diseases on new research of medicine [15]. Immunotherapy vaccines have been established over the last few years, the regulation of cancers and certain non-infectious disorders has been an issue for decades [2-4]. Nonetheless, there have been aplenty confronts and constraints that have averted the production of strong vaccinations against different re-emerging and evolving disorders, like the option of antigens, proper distribution of antigens, and adjunctive infections engineering [16]. To solve these problems, nanotechnology was already utilized, largely comes the vaccine development and production [17][18][19]. Nanocomposite (NC) compounds included in the production of various vaccines are those developed from natural substances such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), inulin, and chitosan alongside synthetic nanoparticles (NPs) like silica-based particles [20].

Synthetic NCs dependent on metals, namely zinc oxide (ZnO), titanium dioxide (TiO2), and iron owing to their complex processes, extended storage life, as well as the capacity to apply their inherent adjuvant-like characteristics and immune-stimulatory functions, oxides have lately been used as vaccine carriers [14]. Owing to the biocompatibility, durability, and lesser cost, Zn, a well-reported Food and Drug Administration (FDA) ratified material, was extensively utilized for many medicinal purposes [21]. In addition, elemental Zn influences many facets of an immune-based response and it could be competently expelled from that body via different channels, like sweat, urine, and feces, thus decreasing the body's effectiveness and the possibility of aggregation [14] [15] inside the body. Nonetheless, an extent of in vivo toxicity and immune reactions have seemed to cause Zn NCs. By generating pro-inflammation cytokines in the myeloid distinction main reaction protein-88 based way through Toll-like receptor (TLR) signal mechanisms when imparted through a pulmonary tract, Zn NPs has become demonstrated to trigger lung infection [17]. Zinc Oxide have a peak effect on the cell surface and initiated when subjected to UV-Vis light to produce ROS, such as hydroxyl radicals, superoxide anion, and hydrogen peroxide. They penetrate the cell body where peroxide ion, ROS carrying negative charge remain on the cell surface. Zinc cation is released when it is triggered by the assembled zinc oxide nanoparticles in the cytoplasm or outer membrane of bacterial cells, which might cause disintegration of cell membrane, membrane protein damage and genomic instability leading to bacterial cell death [22].

Hence this review provides an overview of the biofabrication of Zn NPs by using different biological substrates and mechanisms behind the synthesis. It also discusses the recent applications of Zn NPs reported in past years.

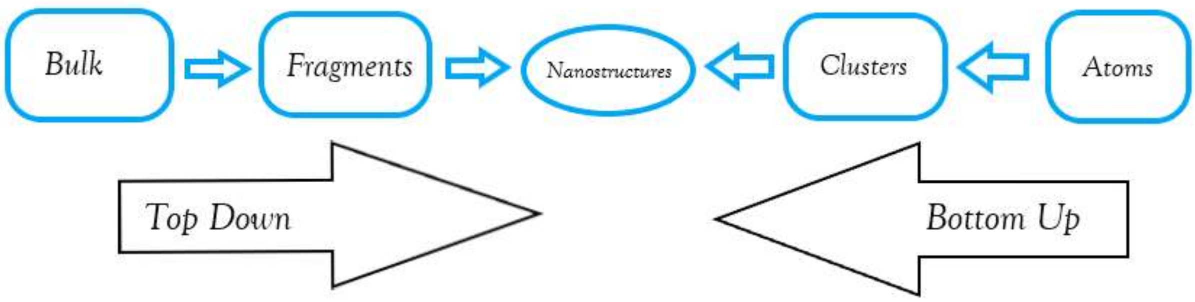

Figure 1. Top-down and Bottom-up approaches of Nanostructures synthesis.

BIOFABRICATION BY USING BACTERIA:

The biological synthesis methods of ZnO NPs are performed by using biologically active products from plants and microbes including bacteria, fungi, and yeast due to their biodegradability and cost-effectiveness, convenience, and high production level [23][24]. Numerous microbes have been employed to produce ZnO NPs, however, bacteria are rapidly outpacing other eukaryotic microorganisms in popularity due to their ease of handling and genetically manipulative nature [25]. The choice of bacteria, ideal conditions for cell growth, and the approach of biosynthesis are essential for the bacterial synthesis of ZnO NPs. To obtain a white powder of ZnO NPs, the ZnO NPs precipitates are repeatedly rinsed with distilled water, followed by ethanol, and then dried at 60 °C overnight. Several physicochemical methods, such as ultraviolet-visible spectroscopy (UV-Vis), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), transmission electron microscopy (TEM), and dynamic light scattering, are used to portray the properties of NPs, like the size, shape, charge density, molecular structure, and purity.

Microbial synthesis may be classified into two types: intracellular and extracellular approach. In the intracellular route, the cell walls of microorganisms and ions charge both contribute significantly to the creation of NPs and ZnO NPs are produced within the cell of microorganisms. Metal ions are absorbed into the cell well and reduced to metal atoms by microbial enzymes. The periplasmic space and cytoplasm then undergo nucleation and proliferation. Through ultra-sonication, the pure nanoparticles are obtained. Bacteria have a variety of polysaccharides and proteins in their cell walls, which act as active sites for binding metal ions [26]. A study by Selvarajan and Mohanasrinivasan reported that *Lactobacillus plantarum* VITES07 produces pure crystalline ZnO NPs with a spherical shape and size ranging from 7 to 19 nm by intracellular biosynthesis. As stated by the authors, the produced NPs with moderate stability functioned as a capping agent in the fabrication process [27].

Regardless the extracellular approach, a nitrate reductase-mediated synthesis, which reduces metal ions into metal NPs, includes either enzyme-mediated synthesis occurring on the cell membrane or the release of the enzyme into the growth medium as an external enzyme. Kundu et al. investigated the role of a secreted protein or enzyme in the synthesis of ZnO NPs by the multi-metal tolerant bacteria *Rhodococcus pyridinivorans* NT2. According to the findings, the produced nanoparticles were nearly spherical, in the hexagonal phase, moderately stable, and exhibited an average diameter of 100–120 nm [28]. Tripathi et al. (2014) discovered that enzymes released by *Bacillus licheniformis* may stabilize ZnO NPs. According to their research, zinc acetate and sodium bicarbonate combine to make $Zn(OH)_2$, which is then thermally reduced to produce ZnO nuclei. The enzymes present in the bacteria will subsequently stabilise the ZnO NPs, limiting agglomeration and particle formation and ensuring the metal oxide's nanoscale size [29]. Further research proved that activated ammonia from ureolytic bacteria (*Serratia ureilytica*) may be used to produce ZnO NPs. The nanoparticle production approach reported in this paper is based on the interaction of zinc ions with ammonia-rich microbe growth conditions, yielding $Zn(OH)_2$ and $[Zn(NH_3)_4]^{2+}$. These compounds are subsequently thermally decomposed at 50°C to provide crystalline ZnO NPs powder [30]. The literature indicates that the extracellular formation is the most common route to produce ZnO NPs using bacteria cultures [30] [31]

Probiotic lactic acid bacteria (LAB) have drawn much attention because of their non-pathogenic and beneficial properties. They have a plethora of bio structures and functional groups that act as a ligand for metal ions, facilitating the synthesis of ZnO NPs [5]. Besides, LAB secretes enzymes and proteins that act as reducing agents and capping agents conferring the stability of ZnO NPs [32]. ZnO NPs with a size range of 5–15 nm were successfully synthesized by Prasad, Jha, Anal, et al. via LABs (*Lactobacillus sporogens*) [33]. Another study by Mahdi, Zahra Sadat et.al. was conducted using the bacterium *Lactococcus lactis* NCDO1281 (T) and *Bacillus sp* PTCC 1538. The results showed that *L. lactis* formed nano-spheres with a diameter of between 55 and 60.5 nm, while *Bacillus sp*. produced nano-rods with an average diameter of 99 nm [34]

The Gram-negative proteobacterium *Halomonas elongata* (strain IBRC-M 10214) was effectively used for the green synthesis of ZnO NPs. The generation of well-dispersed spherical ZnO NPs was demonstrated by FTIR and SEM examination with diameter of 18.11 nm). The ZnO NPs displayed strong antibacterial potential against Gram-positive *S. aureus* ATCC 43300 and Gram-negative *E. coli* ATCC 25922 [35]. In an intriguing research, ZnO NPs were extracellularly bio fabricated using *Aspergillus terreus* AF1, and their biological capabilities were assessed. FTIR examination confirmed that the proteins released by *A. terreus* AF1 served as a capping agent for the ZnO NPs. These spherical ZnO NPs with a size 10-45 nm showed significant antibacterial action against *P. aeruginosa*, *S. aureus*, *B. subtilis*, and *E. coli*, in addition to moderate cytotoxic effect against Vero and Caco cell lines [36].

Sample selection and Zinc solution preparation for biosynthesis are essential and can be accomplished using a range of approaches such as cell biomass (CB) and cell-free supernatant (CFS) route. S. Suba and S. Vijayakumar et al. prepared a stock solution for Zn^{2+} by dissolving Zinc Acetate ($ZnC_4H_6O_4$) in deionized water. The cell biomass was suspended in sterilized deionized water containing 500 mM Zn^{2+} and incubated for 24 hours at 37°C. Following incubation, cells were centrifuged and washed with saline and then disrupted by alternating ultrasonic cycles at 100 W for 5 minutes to get the ZnO nanoparticles, preceded by continuous centrifugation at 5000 rpm for 5 minutes. After being collected using a high-speed centrifuge running at 13,000 rpm for 15 min, the ZnO nanoparticles were then washed with 80% ethanol to get rid of any unwanted components. The ZnO nanoparticles were collected and air-dried at 60 ° C [37].

In another study, both cell biomass (CB) and cell-free supernatant (CFS) were collected for further investigation. A technique identical to that described by S. Suba and S. Vijayakumar et al. was used for the CB route. Meanwhile, the supernatant was employed in the synthesis step for the CFS method. In brief, an equivalent amount of CFS was added to deionized water with 100 mM Zn2+ concentration and incubated overnight at room temperature with 150 rpm agitation until the white solution faded, suggesting the synthesis of ZnO NPs. As a result, the ZnO NPs were recovered by centrifugation (18,000g for 10 min), rinsed with distilled water, and followed by ethanol to remove excess Zn2+ from the reaction mixture before centrifugation. The obtained ZnO NPs were then dried at 100 °C [5].

The next fabrication technique demonstrated by D. Jain et al. involves inoculating *Serratia nematodiphila* strain ZTB15 in Luria Bertani (LB). To this overnight cultivated culture (OD>1 at 600 nm), 0.1 M zinc sulfate was added by drops, heated at 80°C for 10 minutes until a white precipitate emerged at the bottom of the flask, and incubated for 24 hours. ZnO nanoparticles were polished by washing them repeatedly at 14,000 rpm for 10 minutes and dried at 120°C [22].

BIOFABRICATION BY USING FUNGI:

Zinc acts as the second most abundant after iron and it is the only metal represented in the six classes of Enzymes (lysases, transferases, oxidoreductases, hydrolases, isomerases and ligages). Zinc oxide, in both bulk and nanosized form, has been extensively used in the industrial and commercial sphere in large amount [40]. The mobility of zinc nanoparticles and other forms of Zinc in the soil is influenced by factors such as the content and quality of clay minerals, pH of the soil, hydroxides of Al, Fe, Mn and Organic matter present in the soil [38].

Due to its applications, studies on the synthesis, properties and characterization of ZnO NPs have received much attention recent years [38]. Biosynthesis of Zinc nanoparticles using fungi is widely used method to produce monodispersed nanoparticles with wide range of different chemical compositions. Fungi produce large amount of proteins and enzymes and as a result the yield of nanoparticles by fungi produce proteins and enzymes and as a result the yield of nanoparticles is high. Extracellular synthesis of nanoparticles by fungi produce protein stabilized nanoparticles and allows an efficient way to extract nanoparticles from them [39]. Mostly fungi were chosen because of its resistance to process conditions and variations such as pressure, flow rate and stirring which enhance their potential use for large scale synthesis. In comparison to the bacteria synthesis it is believed that the fungus may have superior potential for the green synthesis of nanoparticles. Since, it can release higher concentrations of metabolites to the culture media than bacteria cells [40]. There are wide applications of fungi as they produce huge enzymes, ease in the scale-up process, economic viability, high binding capacity is in handling the biomass [39].

Fungi has been reported to possess secondary metabolites responsible for the antifungal, antibacterial, anti-cancerous properties. Many fungi have been utilized to determine extracellular biomass free production of metal nanoparticles, such as *Penicillium sp*., *Aspergillus sp*. and *Verticillium sp*. [41]. There are two routes by ZnO NPs can produce i.e. extracellular and intracellular synthesis. Extracellular synthesis is enzyme mediated such as nitrate reductase enzyme which is secreted in the medium and reduces metal ions to metal NPs. Zinc Oxide NPs are formed when electrons are transported from NADH by an Enzyme NADH reductase to Zn^{+2} which are reduced into ZnO NPs. In intracellular synthesis, transportation of metal ions within the cell takes place where they are reduced by enzymes present there which leads to increase in nuclei resulting in nanoparticles formation in the periplasmic space and cytoplasm [39].

Mukherjee et al. [42] reported intracellular mechanism for NPs by *Verticillium sp*. Consisting of three steps trapping, bioreduction and capping. The intracellular mechanisms involve the transportation of metal ions in to the cell wall by electrostatic attraction. The metal ions are reduced to metal atom by the enzymes found in the cell wall and then initiate the nuclei growth to form NPs in periplasmic space and cytoplasm. After the intracellular synthesis to obtain the purified Nanoparticles ultrasonication is required. Biosynthesis of ZnO NPs was carried out by using *Aspergillus niger*. In this study, cell free supernatant was used in which 5mM Zinc Nitrate was added and kept in shaking incubator at 32˚C for 2 days followed by precipitation leads to the production of ZnO NPs [43]. Similar study was carried out by using fungal filtrate of *Aspergillus terreus* mixed with 1mM of $ZnSO_4$ for synthesis of Nanoparticles [44].

Production of ZnO NPs by two newly isolated Fungal strain i.e. *Aspergillus niger* strain (G3-1) and *Fusarium keratoplasticum* strain (A1-3). Cell filtrate of this both fungal strain was treated with 2mM zinc acetate $[Zn(CH_3CO_2)_2]$ to form precipitate which was dried at 150˚C for 48h to be used for further investigation [45]. Identical method was used for the synthesis of ZnO NPs by using zinc nitrate hexahydrate $[Zn(NO_3)_2.6H_2O]$ with fungal filtrate of *Xylaria acuta* followed by heating the reaction mixture [42].

BIOFABRICATION BY USING ALGAE:

Algae are photosynthetic organism which ranges from unicellular form [e.g. *Chlorella*] to multicellular ones [e.g. Brown algae]. Algae lack basic plant like structure i.e. roots and leaves. [46]. Active compounds contain functional groups such as hydroxyl and carboxyl groups can be found in different species of algae [40].

Algae have been used extensively for synthesis of Au and Ag nanoparticles but its application for the ZnO nanoparticles synthesis is limited. Microalgae drew special attention because of its ability to degrade toxic metals and convert them to less toxic forms [46]. Although algae are simple organisms, the phytochemical composition of algae can be related to the composition of plant extracts [40]. The edible biomass of algae is rich source of nutraceutical and pharmaceutical biomolecule such as proteins, vitamins, pigments and polysaccharides as well as minerals and it can be used frequently for biogenic synthesis of metal and metal oxide nanoparticles by either intracellular or extracellular mechanisms. Moreover, the rapid growth rates, avoidance of contaminations, and low cost of biomass production of algae is the promising source for the biosynthesis of nanoparticles [47]. Bioreduction of Zinc ions in watery algal medium to ZnO NPs is carried out through donor- acceptor mechanism as a result of interaction between oxygen atoms of biofunctional groups present in algal extract and zinc ions of the salt precursor. Generally, three stages including activation, growth and termination phase could involve in algae – assisted ZnO NPs biosynthesis process [48].

Synthesis of ZnO NPs was carried out by using 80 ml of Zinc acetate solution. Heating treatment was given to accelerate the reduction process by the electron–rich organic biomolecule of microalgae *Chlorella*. In this experiment supernatant of chlorella extract was used for the production of milky solution further processed to synthesize nanoparticles [48]. Similar study was carried out by Sangeetha Nagarajan and her coworkers [49] by using 1mM Zinc nitrate. They used three variant type of fresh and healthy algae extract of *Caulerpa peltata*, *Hypnea valencia* and *S. myriocystum* for biosynthesis zinc oxide nanoparticles. Green synthesis of ZnO NPs was carried out by using 1mM zinc sulphate as a starting material. Algal extract of *Anabaena cylindrica* was added in zinc sulphate solution, pH of the solution being kept at 8.4, followed by drying the solution overnight at 100˚C [50]. This algae has been used for the synthesis of copper oxide nanoparticles for drinking water treatment [51]. Another study was performed by Ehab F. El-Belely and his coworkers in the year 2021 [47], they used 0.44g of Zinc Acetate which was added in biomass filtered solution of microalga *A. plantensis*. The mixture was then incubated for 24hrs in a shaking condition to obtain ZnO NPs as a powder.

BIOFABRICATION BY USING PLANTS:

For biosynthesis of zinc nanoparticles, the most commonly used biomaterials are plant extracts made by using different parts of the plant. The usage of plant extracts in production of nanomaterials began since the early 1900s but the mechanism on nanomaterials production is still not well known and understood [52]. The extract contains various phytochemical compounds such as phenol, alkaloids, tannins, flavonoids, terpenes, saponins and proteins [53]. For production of zinc nanoparticles these compounds can act as capping, reducing and stabilizing agents. Plants are the most common biological substrate used for the green synthesis of nanoparticles with metallic ions [54]. This might be because of the fact that plant substrates are believed to be easier to process, cost-effective, and less toxic than microorganisms. Also, there is no exposure to health risks or concerns about safety issues related to hazardous microorganisms during the process when using plant based substrates. In addition, plant extracts can be easily obtained by exposing the plant part to a solvent, which is usually methanol, ethanol or distilled water. Different parts of the plant have been applied to this purpose such as leaves, roots, seeds and fruits [55]–[57] The antioxidants present in the plants are responsible for the green synthesis of metal or metal oxides nanoparticles due to their capability to bioreduce or chelate metal ions and to act as stabilizers of the produced nanoparticles [58], [59].

Despite the knowledge of the phytochemical properties of the antioxidants, plant extracts are constituted of an enormous variety of these active compounds in different concentrations [60]. Regarding the green synthesis of ZnO NPs, published research suggest in theory that the compounds present in the plant extract react with a zinc salt to reduce or to form complexes with the metal [61]. Although ZnO NPs produced using plant extracts is simple and cost effective, this process still has a few disadvantages such as polydisperse nanoparticles due to diverse phytochemicals and reproducibility of ZnO NPs using seasonal plants as variation of season will lead to variation of phytochemical present in the extracts. In general, the production of ZnO NPs using plant extract has two stages and it began with collection of plant extract. For removing any dust or debris the plant parts are washed and then dried after which the target part is cut into small pieces or crushed into powder form. They were then boiled in water for specific duration to extract the phytochemical out of the plant. The extract was purified through centrifugation or filtration process and this is the end of the first stage. In the second stage, the purified plant extract was mixed zinc salt solution. The phytochemical in the plant extract which contain many hydroxyl groups will form bonds with the zinc ions and this led to a stable complex. Through heat treatment, ZnO NPs is obtained through decomposition of the complex. High temperature of calcination will improve the crystallinity of produced ZnO NPs. Although ZnO NPs produced using plant extracts is simple and cost effective, this process still have a few disadvantages such as polydisperse nanoparticles due to diverse phytochemicals and reproducibility of ZnO NPs using seasonal plants as variation of season will lead to variation of phytochemical present in the extracts.

Many researchers have used different salts of zinc for the synthesis of Zinc nanoparticles but Zinc Acetate and Zinc Nitrate were used substantially. Muthukuramaran A. et al. [62] proposed a mechanism route based on the chemical characteristics of the flavonoids, limonoids and carotenoids that constitute the leaves of *Wattakaka volubilis* used for obtaining the ZnNPs. In this work, these antioxidants are believed to chelate the zinc ions and form metal coordinated complexes that are further thermally treated to degrade the complex and form zinc oxide with an average size of 9.7 nm. Chauhan P.K. et al. [63] established a similar mechanism where the antioxidants of *Carica* Papaya leaves also chelate the zinc (II) ions which formed zinc oxide after a calcination process. In this work, the plant extract and ZnNPs obtained with different temperatures treatment (100 °C and 500 °C) were analysed using Fourier transform infrared spectroscopy (FTIR). It is also proposed that the plant compounds act as stabilizers preventing agglomeration of particles and crystal growth [61]. Likewise, Hasnain Jan et al. [64] proposed the bioreduction of zinc (II) ions by ascorbic acid when using *Aquilegia pubiflora* extract to obtain ZnNPs. Jayachandran A. et al. [65] biosynthesized ZnNPs using plant extract and suggested that the metabolites that compose the substrate are responsible for both the reduction of the metallic ions and particle stabilization. It is interesting to observe that, for metal nanoparticles, the mechanism route of metal complexation requires a thermal treatment to obtain the nanoparticles. In contrast, the metal bioreduction produces the colloidal nanoparticle with the plant extract without further treatment.

APPLICATIONS:

The Food and Drug Administration currently lists ZnO as a "generally regarded as safe" (GRAS) substance, and it is also used as a food additive. ZnO nanostructures have a strong catalytic efficiency as well as great adsorption ability and are increasingly used in the production of sunscreens. In particular, zinc oxide (ZnO) nanoparticles distinguish among other metal oxide particles due to the wide range of functions it possess, including as a gas sensor, biosensor, cosmetic, storage, optical device, window material for displays, solar cell, and drug delivery system.

Antimicrobial Activity:

The antibacterial potential of 'Nanomaterials' stem from their unique traits, such as high reactivity and a large surface area to volume ratio, which permit them to interact with a large number of ligands on the Nanoparticles surface and thus interact with receptors present on the bacterial surface[37]. It is widely understood that zinc oxide nanoparticles exhibit antibacterial properties and can easily penetrate into the cell membrane preventing the growth of bacteria. Oxidative stress causes significant damage to lipids, carbohydrates, proteins, and DNA [22]. The antibacterial mechanism of ZnO NPs involves direct communication between ZnO nanoparticles and cell surfaces, which affects cell membrane permeability; eventually, nanoparticles invade and trigger oxidative stress in bacterial cells inhibiting cell growth and proliferation. ZnO NPs were found to be harmful to pathogenic bacteria (e.g., *E. coli* and *Staphylococcus aureus*) also have therapeutic action against *Pseudomonas putida*, a vigorous root colonizer with bioremediation potential [66]. It has been found that the smaller size of zinc oxide nanoparticles displays greater antibacterial activity than micro scale particles. Jones et al. [67] revealed that 8-nm zinc oxide nanoparticles hindered the growth of *E. coli, S. aureus* and *B. subtilis*. ZnO NPs with diameter varying between 12 to 307 nm were examined, and the correlation between antibacterial activity and size was validated. Their toxicity to microbes has been attributed to the formation of Zn^{2+} ions from zinc oxide when suspended in water, and to a smaller extent to pH change. However, Zn^{2+} ions are scarcely released from zinc oxide nanoparticles, the antibacterial activity is primarily due to smaller ZnO NPs. Overall, NP with size 12 nm inhibits the growth of *S. aureus*, but as the size exceeds 100 nm minimal inhibitory effects is observed.

Anticancer applications:

Cancer is a group of diseases defined by abnormal tissue growth that can lead to the formation of tumors that can spread into other tissues and cause significant consequences in the patient, with complications and severities possibly resulting in death. ZnO has been explored for anticancer therapy in recent years. Zinc is present in the body as an important trace element as a result; it does not frequently impair cell viability. ZnO NPs, on the other hand, are known to trigger the advent of ROS as they interact with cells, which lead to mitochondrial damage and cell death in cancer tissue [68]. According to Bai et al., ZnO NPs with a crystal size of 20 nm resulted in a concentration-dependent loss of ovarian cancer SKOV3 cell viability. Furthermore, ZnO NPs administration of SKOV3 cells resulted in an increase in LC3-I/II and p53 expression, which further triggered autophagic cell death [69]. Arakha et al. applied the chemical precipitation approach to create ZnO NPs and then assessed their anticancer efficacy, uncovering that ZnO NPs of varying sizes could clearly suppress the growth of fibrosarcoma HT1080 cells. The findings showed a connection between intracellular ROS production and the incidence of autophagy in cancer cells. The interaction of ZnO NPs with the HT1080 cell produces much more ROS. Excessive ROS led Biomolecular damage, including DNA damage, and ultimately cell death [58].

ZnO nanoparticles were biosynthesized by Moghaddam et al. employing a yeast strain, *Pichia kudriavzevii* GY1 and their anticancer efficacy was assessed in breast cancer MCF-7 cells. It showed strong cytotoxicity against MCF-7 cells, which was linked to the incidence of apoptosis rather than cell cycle arrest. ZnO NPs-induced apoptosis occurred primarily via both extrinsic and intrinsic apoptotic pathways, with certain anti-apoptotic genes such as

Bcl-2, AKT1, and JERK/2 being down-regulated and pro-apoptotic genes such as p21, p53, JNK, and Bax being up-regulated [70]. In a sophisticated work, Padalia et al. produced spherical and irregularly shaped ZnONPs using a leaf extract from *Ziziphus nummularia*. The structures were evaluated in a range of 2 to 200 g /ml and substantially reduced cervical cancer cell viability by 60% [71]. Another example was the use of *Laurus nobilis* leaf extracts in the production of ZnO NPs (through co-precipitation technique), which successfully inhibited pulmonary cancer cell growth at dosages of 80 g/ml without hampering health of murine RAW264.7 macrophage cells [72].

Tissue engineering and wound healing applications:

In addition to antibacterial and anticancer capabilities, ZnO nanostructures have antineoplastic, wound healing, UV scattering, and angiogenic properties that are frequently used in tissue engineering applications [37], [73]. The application ZnO NPs in tissue engineering has become an even more specialized field. Nonetheless, a few examples have arose in recent years introducing the idea that ZnO NPs pro-angiogenic capabilities can be particularly valuable in promoting scaffold integration to host tissue. However, a much broader understanding of the mechanism of their selective cytotoxic activity, together with a lack of acceptable biocompatible dispersion methods, is needed in the future. Shubha et al. [74] described the utilization of ZnO NPs produced by gallic acid, extracted from *Phyllanthus emblica* aqueous extract. Their products' physical, chemical, in vitro, and in vivo toxicity were compared to those of therapeutically recommended ZnO NPs. The researchers employed balb mice 3T3 fibroblasts in vitro as one of the major connective tissue cells (which assist in tissue repair and regeneration).

Compared to commercially available nanostructures, green synthesized ZnO NPs were less hazardous at the greatest concentration, according to the in vitro and in vivo studies. This discovery shows that ZnO NPs might be a viable choice for use near connective tissue cells. Similarly, Kumar et al. developed chitosan hydrogel micro porosity bandages laced with zinc oxide nanoparticles, which are particularly successful in healing burns, wounds, and diabetic foot ulcers among all natural and synthetic wound dressing materials. On the surface of the bandage, nanoparticles measuring 70-120 nm are distributed [75]. Yadav et.al. [76] evaluated the efficacy of *Trianthema portulacastrum* Linn produced ZnO NP with diameters ranging from 10 to 20 nm. An in vitro anti-inflammatory activity study of the nanostructures was performed using membrane stabilization and albumin denaturation (along with proteinase inhibitory assays), resulting in a significant wound contraction rate, epithelialization, and histopathology of the healed tissues of rats, confirming the nanostructures' promising wound healing property. Furthermore, inflammatory biomarkers and the antioxidant enzyme profile support their wound healing ability, indicating a potential utility in wounds via antioxidant and anti-inflammatory action [76].

Drug Delivery with ZnO nanoparticles:

ZnO nanoparticles are ideal Nano platforms for drug delivery applications because of their extensive surface area, adaptable surface chemistry, and phototoxic effect, among other properties. According to in vitro research, ZnO nanoparticles can be extremely hazardous to bacteria, leukemic T cells, and cancer cells. As a result, ZnO nanoparticles have been researched not just as drug/gene delivery vehicles, but also for cancer treatment [37]. ZnO QDs with intrinsic blue fluorescence were electrostatically coated with folate-conjugated chitosan, which could be loaded with doxorubicin (DOX, a commonly used chemotherapeutic medication) with 75% efficiency. DOX was entrapped by hydrogen bonding with the surface of ZnO QDs and/or folate, whereas the exterior chitosan layer facilitated water stability of the ZnO QDs due to charges and hydrophilicity. However, DOX was readily released at the standard physiological pH of 7.4, which has to be addressed for future in vitro/in vivo experiments [77].

Recently, Fe3O4-ZnO core-shell nanoparticles with an average diameter of 16 nm were developed to transport carcino-embryonic antigen into DCs and might also be used as imaging contrast agents. In vitro, antigen-bound nanoparticles were readily taken up by DCs, with the ZnO shell facilitating cell internalisation and greatly reducing the time required for labelling DCs. There were no changes in viability or phenotypic in the nanoparticle-labelled DCs. More crucially, MRI effectively identified the uptake of nanoparticle-labelled DCs in mice draining lymph nodes, indicating that these nanoparticles might be used for image-guided antigen delivery and in vivo surveillance of the loaded DCs in the future [1]

Bio imaging with ZnO nanoparticles:

ZnO NPs have effective blue and near-UV emissions with green or yellow fluorescence associated to oxygen vacancies, extending its applicability into the bio imaging domain [85]. Within human hepatoma cells, ZnO-1 (produced from LiOH) with an average size of 3 nm fluoresced green, while ZnO-2 (derived from NaOH) with an average size of 4 nm fluoresced yellow. It's noteworthy that at concentrations less than 0.2 mg/mL, these nanoparticles had no visible toxicity for human hepatoma cells. Furthermore, the luminescence was quite steady throughout cell culture, and the cells were still alive after 45 minutes. The fluorescent probes formed from ZnO@polymer core-shell nanoparticles could be applied for in vitro cell imaging as a form of safe and cost-effective luminescent labelling [78]. The invasion of ZnO nanoparticles in human skin was visualized in vitro and in vivo using their intrinsic fluorescence [79]. It was discovered that the majority of ZnO nanoparticles remained in the stratum corneum, with limited possibility of causing safety problems. Another work created biocompatible ZnO Nano crystals (NCs) with nonlinear optical characteristics, enclosed them within the nonpolar core of phospholipid micelles, and coupled them with folic acid (FA) for nonlinear optical microscopy [80].

Optical properties:

The intrinsic optical characteristics of ZnO nanostructures are being thoroughly investigated in order to develop photonic devices. The photoluminescence (PL) spectra of ZnO nanostructures have received great attention. According to the photoconductivity analyses of ZnO nanowires, the presence of O_2 has a significant influence on the photo-response. The photo response of ZnO nanowire was discovered to be affected by the desorption-adsorption process of O_2. Photo generated holes discharge surface chemisorbed O_2 via surface electron-hole recombination when illuminated; whereas photo generated electrons considerably improve conductivity. When the light is turned off, O_2 molecules reabsorb on the nanowire surface and decreased conductivity [81].

Textile Industries:

The application of zinc nanoparticles in textiles is growing rapidly, since it can provide unique properties to the textile, such as antimicrobial activity, photocatalytic self-cleaning, UV protection, thermal insulation, flame retardancy, and moisture management, hydrophobicity, and electrical conductivity. The extraordinary photocatalytic activity, chemical stability under UV radiation exposure, thermal stability, and absorption of a broad range of UV radiation allow ZnO particles (ZnO Ps) to be one of the most effective photocatalytic self-cleaning, antimicrobial and UV-protective agents. Furthermore, ZnO Ps have been applied to textile fibers to improve flame retardancy and thermal stability and to achieve moisture management and thermal insulation, electrical conductivity, and hydrophobicity [14]. The photocatalytic properties also enable ZnO Ps to be used as degradation agents for different pollutants, such as dyes and surfactant present in textile industry wastewaters [15]. The self-cleaning properties of ZnO Ps are derived from their photocatalytic performance. If ZnO Ps are present on the surface of textile fibers, ZnO is capable of photocatalytic degradation of various organic colorless or colored dirt stains when it comes in contact with them. The UV protection properties of ZnO are derived from its excellent chemical stability under UV radiation exposure and high effectiveness in locking both UV-A and UV-B radiation [21]. For human skin protection against UV irradiation, ZnO has mostly been applied to woven and knitted cotton fabrics, since natural cellulose fibers are usually used for the tailoring of light summer protective clothing. The presence of ZnO on fibers can contribute considerably to the wear comfort performance of textiles, since it can significantly increase the thermal insulation and improve the moisture management capability of fabrics. Accordingly, a cotton fabric with increased thermal insulation for cold weather clothing was created by covering the pores of twill woven fabric using a ZnO coating [16]. Consequently, the resistance to evaporative heat loss increased and the water vapor permeability of the fabric decreased significantly.

It has been proposed that the fame retardancy of ZnO is based on a condensed phase mechanism of action via the heat barrier effect. As a highly thermally stable inorganic material, ZnO can protect the insulation layer on the fiber surface, which reduces the transfer of heat, fuel, and oxygen between the fame and fibers and consequently reduces the rate and intensity of combustion. ZnO has already been designated as a smoke suppressant. For textile applications, the hydrophobic behavior of ZnO NPs is less relevant, since the hydrophilic self-cleaning activity of ZnO with a high water absorption capacity is increasingly exploited [19]. It was found that the synthesis conditions directly influenced the morphology of ZnO crystals size which ultimately impacts the hydrophobicity/hydrophilicity of cotton fabric. Dual properties of zinc oxide i.e. semiconducting and piezoelectric brought up the idea that it can be used for the fabrication of wearable/textile electronics. Namely, the high piezo-photocatalytic efficiency enables ZnO to convert mechanical and solar energies into electricity, which is crucial for smart textiles.

Zinc Nanoparticles in Agriculture:

Nanotechnology has a dominant position in transforming agriculture and food production. Nanotechnology has a great potential to modify conventional agricultural practices. Most of the agrochemicals applied to the crops are lost and do not reach the target site due to several factors including leaching, drifting, hydrolysis, photolysis, and microbial degradation. Nanoparticles and nanocapsules provide an efficient means to distribute pesticides and fertilizers in a controlled fashion with high site specificity thus reducing collateral damage. Farm application of nanotechnology is gaining attention by efficient control and precise release of pesticides, herbicides, and fertilizers

Zinc oxide nanoparticles (ZnO NPs) have remarkable optical, physical, and antimicrobial properties and therefore have great potential to enhance agriculture. As far as method of formation is concerned, ZnO NPs can be synthesized by several chemical methods such as precipitation method, vapor transport method, and hydrothermal process. The biogenic synthesis of ZnO NPs by using different plant extracts is also common nowadays. This green synthesis is quite safe and ecofriendly compared to chemical synthesis [81].

Zinc oxide NPs have potential to boost the yield and growth of food crops V. Prasad et al., [82] showed the effect of ZnO NPs of different concentration for the growth of peanut seeds. Zinc oxide nanoscale treatment (25 nm mean particle size) at 1000 ppm concentration was used which promoted seed germination, seedling vigor, and in turn showed early establishment in soil manifested by early flowering and higher leaf chlorophyll content, zinc oxide nanoparticles also proved to be effective in increasing stem and root growth in peanuts. Salinity is a significant problem that limits plant growth and development and dramatically reduces crop production. In the present study, it demonstrated the changes in genetic template stability and cytosine methylation caused by salinity stress in tomato plants treated with ZnO-NPs at both levels (20 and 40 mg L−1), with different Plant Growth promoting bacteria (*Bacillus subtilis*, *Lactobacillus casei*, and *Bacillus pumilus*), under NaCl stress, this study revealed the protective role of Zinc Oxide Nanoparticles and PGPB significantly reducing cytosine hyper methylation and negative effect on DNA damage [83]. The colloidal solution of zinc oxide nanoparticles is used as fertilizer. This type of nanofertilizer plays an important role in agriculture. Nanofertilizer is a plant nutrient which is more than a fertilizer because it not only supplies nutrients for the plant but also revives the soil to an organic state without the harmful factors of chemical fertilizer. One of the advantages of nanofertilizers is that they can be used in very small amounts. An adult tree requires only 40–50 kg of fertilizer while an amount of 150 kg would be required for ordinary fertilizers [82].

In this study, Foliar fertilization is performed by using Zinc salts or Chelates. Pecan trees grafted to native seedlings were treated with ZnNo3, Zn EDTA and Zn DTPA compared with the Zn untreated control. After 3yrs of evaluation, the trees with best appearance were those treated with $ZnNO_3$ and Zn DTPA which shows Zn concentration increased by 73% & 69% when compared with the control which shows 37% lower under Zinc deficiency conditions [84]. Similar study was performed by using different concentration Salicylic acid (0, 50, 100 & 150ppm) and Zinc (0, 300, 400 & 500 ppm) Combination of SA and Zinc increase the seed weight plant, No. of pods plant, No. of branches plant, plant height when compared with control (Untreated plant) [85].

Zinc Nanoparticles in Food Industry:

Bioactive components with antimicrobial activity against food pathogens are encapsulated into nanoparticles (NPs) to improve and extend their efficiency in food preservation. However, these NPs should be biocompatible and nontoxic for humans. Advancement in this field has resulted in the development of NPs for food packaging in some industries. The most commonly used group of NPs in the food industry is metal oxide. As metal oxide NPs such as zinc oxide exhibit antimicrobial activity in food materials, the NPs can be used for food preservation with enhanced functional properties [86].

Studies have been carried out to examine the antibacterial activity of ZnO nanoparticles and the viability of the bacteria under ZnO applied conditions. When it is reduced to nanometer size it has been found in many studies that ZnO acts as an antibacterial agent. ZnO nanoparticles react with the surface and core of the bacteria, thus causing a bactericidal effect. Xie et al.,[87] demonstrated in their study that when *Salmonella enterica*, *Enteridis*, other *Salmonella strains*, and *E. coli* O157:H7 were exposed to a lower concentration of ZnO nanoparticles with size 30 nm, a total of 100% bactericidal effect was observed. These nanoparticles also show high photochemical activities and catalytically activities along with antibacterial and antifungal properties. As ZnO absorbs UVA in the range of 315–400 nm and UVB in 280–315 nm, it enhances the antibacterial responses [88]. In one of the studies, it was observed that when UV coincides with ZnO nanoparticles it produces reactive species such as hydroxide, hydrogen peroxide, and superoxide anions, which causes damage to cellular components, i.e. lipids, proteins, and DNA, leading to internalization of cell membrane of bacteria [89].

A study was carried out to develop packaging films made up of agar incorporated with zinc nanoparticles to improve mechanical and functional properties. Being transparent and flexible, agar can be used to synthesize packaging films. ZnO nanoparticles were made from the extract of plant *Mimusops elengi* and added to the agar matrix. The effectiveness of the package was evaluated by observing the external features of packaged green apples in the agar-nanoparticles based packaging material under ambient conditions. Two packaging films were prepared with 2% ZnO nanoparticles and 4% ZnO nanoparticles. Green grapes wrapped in plastic (polyethylene) film spoiled after 7 days due to mold development and leaking of sticky liquid, but fruits wrapped in agar-ZnO films with 2% ZnO nanoparticles remained fresh even after 14 days and for 21 days when wrapped in films with 4% ZnO nanoparticles [88]. Another study was carried out in which ZnO NPs combine with gelatin- based composite films results in significant antibacterial activity against Gram-positive and Gram-negative food pathogens [90].

CONCLUSION

Nanoparticles are an imminent area of research due to their limited size of less than 100nm. The preparation of metallic nanoparticles using a green method is cheap, environmentally friendly and easily scaled up compared to other methods. Numerous studies report the possibility of obtaining ZnO NPs through a green synthesis process using a variety of plants, fungus, bacteria and algae. Moreover, the studies cited here indicate that these substrates act as reducing and stabilizers or as chelating substances despite its source. It is interesting to notice that besides the difference between the compositions found in biological extracts, parameters such as conditions of temperature, time of reaction, pH and concentrations, significantly alter the final properties of the synthesized nanoparticles. According to the literature cited and among these parameters the concentrations of both zinc source, biological extract and also the pH of the solution play a crucial role on the final properties of zinc nanoparticles obtained using the green route.

Although the complexity of biological substrates still poses a challenge to evaluate the green synthesis of nanoparticles, further investigations on the mechanism of formation of the biological synthesis of ZnO NPs are necessary to achieve a better understanding of the chemical processes and reactions that occur during the synthesis. It seems that with the designation of the mentioned mechanism, it will be possible to control and optimize the green synthesis process, which is essential for the large scale production of ZnO NPs. Thus ZnNPs are considered as a potential platform for biomedical research due to their various properties which was summarized above.

Conflict of Interest: None

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