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[Review Article]

Green Synthesis and Biomedical Applications of Zinc Oxide Nanoparticles

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IN THE past ten years, biomedical nanomaterials have attracted a lot of attention. Because of their extensive and significant biological features and biomedical uses, they have underlined several issues. There are many medical applications for metal oxide nanoparticles, including antibacterial, drug/gene delivery, anticancer, cell imaging, and biosensing. In recent years, a variety of industries, including the pharmaceutical, cosmetic, concrete, antibacterial, and textile industries, as well as the automotive industry, have used zinc oxide nanoparticles (ZnO NPs) as a major material. The potential of ZnO NPs to create reactionary oxygen species and initiate cell programmed (apoptosis) is associated with anticancer and antibacterial activities. So, in order to meet the increased demand for ZnO NPs, numerous synthetic techniques have been used to produce them. There is now a search for additional alternatives with environmental and financial advantages due to the economic and environmental costs associated with the majority of ZnO NP production methods. It's interesting that the biological technique of synthesis, which uses plants, plant extracts, or microbes as sources, has been proven suitable for the creation of ZnO NPs because of its multiple medical, health, environmental, and economic advantages. This review summarized the most current developments in the synthesis and biomedical uses of ZnO NPs made using green synthesis.

Keywords: Zinc oxide nanoparticles, Green synthesis, Biomedical applications, Antidiabetic, Antimicrobial and anticancer, Biosensors.

Introduction

Metal and metal oxide nanoparticles have shown wide applications in numerous fields such as agriculture, pharmacy, catalysis, medicine, textile, heavy industry dealing with consumer goods, and antimicrobial assay [1-4]. Zinc oxide nanoparticles (ZnO NPs) are used extensively in a number of sectors owing to their distinct physical and chemical properties5]]. Zinc oxide nanoparticles also possess exceptional UV blocking qualities, antimicrobial and antibacterial. This resulted in finished textiles with ZnO NPs that have desirable antibacterial, deodorant qualities and UV and visible light resistance [6]. Natural

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zinc is necessary for human, animal, and plant metabolism [7]. Zinc is a well-known essential trace element featured in all physiological tissues, along with bone, muscles, skin and brain. Zinc oxide is a widely utilized substance with advantageous dietary supplement properties as well as applications in pharmacology, cosmetics, and medicine. Although breathing in zinc oxide dust and fumes is typically not advised, it is possible. [7] Although most ZnO used for commercial purposes is manufactured, it can be revealed as the mineral zincite in the earth›s crust by including. Zinc oxide in products and surfaces that come into contact with skin, ZnO is rendered safe for use and pleasant for human skin. Zinc oxide nanoparticles are widely used in many different industries, including photocatalysts [8, 9], ethanol gas sensors [10, 11], UV light-emitting devices [12, 13], the pharmaceutical industry [14], and the cosmetics industry. Zinc oxide nanoparticles are harmless, self-cleaning, and kind to the skin, among other benefits. Due to its antimicrobial and dermatological effects, UV blockers are used in sunscreen and many medical specialties [15]. According to numerous studies, ZnO appears to have a strong antimicrobial defense, and also, all three oxides—Ca, Mg, and Zn—display strong antibacterial pharmacological action [16].

Many researchers have employed zinc oxide nanoparticles as a drug delivery system for a lot of disorders. These nanoparticles› ability to deliver drugs to various cells and tissues has been proven [17, 18]. Zinc oxide nanoparticles have the potential to be used as a bioimaging device. They are also less dangerous than other metal oxide NPs and are priced reasonably. Zinc oxide nanoparticles are effective sunscreen agents due to their strong ultraviolet (UV) absorption and transparency for visible light [19, 20].

Due to their propensity to produce ROS, additional characteristics, such as antibacterial and anticancer effects, have also been researched [21]. In addition to possessing inherent biological characteristics, Zinc oxide nanoparticles are efficient drug carrier systems. Zinc oxide in bulk has also received United States Food and Drug Administration (FDA) approval as a generally recognized as safe (GRAS) material, and zinc oxide nanoparticles larger than 100 nm are deemed to be biocompatible, suggesting they could be utilized to deliver pharmaceuticals [22]. The use of ZnO nanoparticles as an efficient drug delivery method is one of their primary applications [5]. Zinc oxide nanoparticles have been used as drug delivery systems in a number of papers recently for treating various ailments. These nanoparticles' ability to target drugs to different cells and tissues has been demonstrated [5]. Sensing and imaging are other crucial areas in the surveillance and supervision of patients. Zinc oxide nanoparticles might work well as a bioimaging technique. The synthesis of ZnO NPs using biosources as a reducing agent has generally been accepted by researchers among the various approaches and protocols used [23] because it is eco-friendly, uses non-hazardous reagents, is simple to carry out, uses little energy, and is cost-effective. It has been reported that biomolecules and secondary metabolites found in plant extracts, such as tannins, flavanones, saponins, polyphenols, alkaloids, and terpenoids, are responsible for the efficient reduction of zinc precursors; when compared, the effectiveness of plant extracts in this regard was higher than that of microorganisms [24]. Zinc oxide NPs mediated from plant extracts have superior antibacterial activity against bacterial and fungal diseases and human pathogens [25]. Numerous plants, including Trifolium, Justicia adhathoda, Physalis alkekengi L, Cassia auriculata, pretense flowers, Aloe barbadenis, Pongamia pinnata, Limonia acidissima, Plectranthus amboinicus, Cochlospermum religiosum, Sedum alfredii Hance, Aspidoterys cordata, and Bauhin were employed [1, 26, 27]. Therefore, detailed scientific information on current advances in the environmentally friendly synthesis of ZnO NPs and their potential uses in medicine were offered.

Synthesis of ZnO nanoparticles using green methods

Strategies for chemical and physical synthesis are expensive and take a lot of time and effort. In addition, massive amounts of secondary waste are produced as a result of the operations' inclusion of chemical agents for precipitation and reduction. Common chemical processing techniques, like chemical precipitation, produce some hazardous chemical species that adhere on surfaces and have negative consequences in applications for healthcare [21]. Some reactions require air mass and/or heat to begin, while others require an unreactive atmosphere to protect them, as well as the use of deadly substances like H_2S, poisonous models and stabilizers, and bimetallic precursors [22]. The substances employed to synthesize and stabilize nanoparticles are toxic and produce

unfriendly byproducts [28]. Massive amounts of nanoparticles can be created quickly and very cheaply using a variety of physical and chemical processes [29-31]. Solvent-based procedures, such as solvothermal [32], hydrothermal [33, 34], sol-gel [35, 36], chemical precipitation [37], and others, are among the most widely used methods for making ZnO nanoparticles. Some poisonous compounds produced by chemical approaches are absorbable on the surface and have harmful consequences when used in medicine. Growing concern of basic chemistry as well as other biological processes has led to the development of an environmentally benign method for the manufacture of nanoparticles.

The green synthesis of nanoparticles uses reagents that are safe, non-toxic, and kind to the environment. Gelatin was utilized as a stabilizing ingredient by Khors and Zak *et al.* when they changed the sol-gel process to create ZnO nanoparticles. Zinc oxide nanoparticles were stabilized, and their expansion was stopped using long-chain gelatin compounds. The hexagonal (Wurtzite) structure of the ZnO nanoparticles that were calcined at radically diverse temperatures was seen in particles with diameters ranging from 30 to 60 nm. Additionally, the impact of oxidation temperature on the shape of ZnO nanoparticles was examined. According to their findings, gelatin is an amazing substance that can be employed as a stabilizer in the sol-gel process to create tiny ZnO nanoparticles [38] In biological (green) methods, plants, plant extracts, or microorganisms are employed to produce nanoparticles as potential environmentally friendly substitutes for chemical and physical processes. The manufacture of nanoparticles uses a variety of biological processes, comprising fungi, bacteria, and yeast [38, 39]. Microorganisms are used in the synthesis of nanoparticles, which requires complex techniques for sustaining cell cultures, the creation of living things, and numerous purification stages [40]. The employment of "green" approaches during the development of ZnO nanoparticles in a flower-shaped form has drawn more attention because of the high cost and necessity of using chemical/organic solvents as reducing agents in conventional chemical processes [7].

Zinc oxide nanoparticles are one of the prospects for the creation of medical alcohol biosensors [41] since they have deodorizing and drug-like qualities and are used in food packaging. A variety of ZnO nanoparticles are used in products such as mineral creams, barrier creams, anti-dandruff shampoos, and antibacterial ointments, to treat diaper rashes and medical bandages to cure skin disorders in powder [42]. In recent years, ZnO nanoparticles have been utilized in numerous industrial sectors, along with the pharmaceutical, cosmetic, concrete, anti-microbial, textile, and automotive industries [43]. In both microscale and nanoscale formulations, ZnO nanoparticles are now being researched as potential antibacterial therapeutics. According to research, ZnO nanoparticles exhibited antibacterial effects that are reportedly bigger than microparticles [44].

The use of environment friendly materials for the synthesis of ZnO nanoparticles, such as algae [45], bacteria [46], fungi [47], plant leaf extract [48, 49] and natural materials and biopolymers [50], offers a number of benefits in terms of greener and suitability for pharmaceutical and other medical applications, while toxic chemicals are not utilized. Attention has been given to the use of plant extracts in synthesis approach as a simple and workable alternative to chemical and physical approaches. Due to its greener, promising economic future, and practical and extensive range of applications in nanomedicine, chemically altered pharmaceuticals, nano optoelectronics, etc., the «green» technique for nanoparticle manufacturing has gained interest [51]. It is a new and expanding area of study in the scientific community, and daily advancements are noticed, guaranteeing a promising future for this topic. The flower shaped Zinc oxide nanoparticles created by biosynthetic and environment friendly technologies are thought to be non-toxic, biosafe, and biocompatible and are employed as fillers in medical materials, cosmetics and drug carriers [52]. It should be emphasized that the majority of ZnO nanoparticles used in industry are manufactured synthetically and offer several benefits over silver nanoparticles, including reduced cost and a whiter look [53]. One approach for amateurs to create ZnO nanoparticles uses plant extract. Aloe barbadensis miller leaf extract was used by Sangeetha *et al.* for the chemical and biological synthesis of ZnO nanoparticles. Zinc nitrate and Aloe vera leaf extract are used to produce extremely stable and spherical ZnO nanoparticles. More than 95% of the nanoparticles in aloe vera leaf broth were converted at concentrations higher than 25%. Zinc oxide nanoparticles were poly-dispersed, as shown by the scanning electron microscope (SEM) and transmission electron microscope

(TEM) analyses, and as a result, their average size ranged from 25 to 40 nm. Since the produced nanoparticles are overwhelmingly spherical, the particle size can be altered by varying the leaf broth solution's concentration [54].

Zinc oxide nanoparticles biosynthesis using plant mediation

An alternative to the physical and chemical procedures for producing nanoparticles is the synthesis of biological nanoparticles. Most of the research focused on environmentally friendly ways to create metal and oxide nanoparticles. Plants can be used to quickly and cheaply create nanoparticles that are safe for human consumption [55]. So, in order to synthesize ZnO nanoparticles (ZnO NPs) from zinc acetate dihydrate using plants, Tu Uyen Doan Thi *et al.* used an aqueous orange peel extract as a biological reduction agent. It was discovered that physical and chemical factors such the annealing temperature and pH during NP production had a substantial impact on the size and shape of the ZnO NPs [56]. When Khors and Zak *et al*. modified the sol-gel procedure to make ZnO NPs, they used gelatin as a stabilizing component. Long-chain gelatin compounds were used to stabilize ZnO NPs and inhibit their growth. Particles with sizes ranging from 30 to 60 nm were found to have the hexagonal (Wurtzite) structure. These ZnO NPs were calcined at a variety of dramatically different temperatures. In addition, the effect of oxidation temperature on ZnO NPs' form was investigated. According to their research, gelatin is a remarkable ingredient that may be used as a stabilizer in the sol-gel process to produce microscopic ZnO NPs. [43].

Brassica oleracea L. var. italica extract was used to create ZnO NPs, and Osuntokun *et al.* investigated how they are synthesized. It was discovered that Zn(II) ions in $ZnCl_2$ may react with the hydroxyl functional groups on the phenolic moiety on quercetin in *Brassica oleracea* L. var. italic to generate $Zn(OH)_2$. The $Zn(OH)_2$ was then dried in an oven at 70 °C before being calcined in a muffle furnace at 450 °C to create ZnO NPs [57].

From polyphenol-rich pepper extracts, Mercedes Jiménez-Rosado *et al*. synthesized ZnO nanoparticles. Using a response surface analysis, the total polyphenol content (TPC) and antioxidant activity of the extracts have been estimated for the different parameters involved in the polyphenol extraction process (i.e. temperature, extraction time, amount of pepper and solvent used, type of solvent, and part of the pepper used -whole fruit, pulp, or waste). Zinc oxide NPs are formed by colloidal precipitation using the best extracts. When the outcomes of the green NPs were contrasted with those created using chemical reagents, it was found that the green NPs were both purer (having 100 and 88% ZnO content, respectively) and smaller (having 24–43 and 35–70 nm, respectively)[58]. Additionally, ZnO NPs were synthesized and stabilized using the aqueous extract of Solanum rantonnetii leaves at room temperature. The outcome demonstrated that spherical ZnO NPs with diameters ranging from 5 to 12 nm are formed [59].

Using thyme plant leaves as the starting material, Synthesized ZnO NPs in an environmentally friendly manner. The effect of various calcination (annealing) temperatures on the distinguishing characteristics of manufactured ZnO NPs as well as the ideal calcination temperature for developing ZnO NPs were investigated and reported. 150, 250, 350, and 450 °C were the calcination temperatures that were examined. Field emission scanning electron microscope (FESEM) imaging results revealed that the calcination temperature has a strong and substantial impact on the morphology, size, form, and orientation of ZnO NPs, which have a spherical shape and an average size in the range of 39.4-51.86 nm. Additionally, the X-ray diffraction (XRD) data demonstrate that the produced ZnO NPs have a wurtzite hexagonal structure and pure ZnO, with particle sizes along the (002) peak ranging from 35.20 to 243.3 nm. Results from UV-Vis measurements of ZnO nanoparticles showed a significant peak for all ZnO NPs made at various calcination temperatures, a high absorbance in the UV area below 400 nm, and a low absorbance rate in the visible range. In the range of 2.645–2.7 eV, the energy band gap (E_g) was attained. Additionally, the FT-IR spectra of ZnO nanoparticles at various calcination temperatures showed no apparent peak in the monitoring range, demonstrating the purity of the ZnO nanoparticles produced using thyme leaf extract. Additionally, according to all of the results of the synthetic ZnO NPs, the ZnO NPs produced at 450 °C for calcination had higher quality and performance than those produced at other calcination temperatures [60].

The leaf extracts of the Pinus Brutia (PB) tree have also been used to create zinc oxide (ZnO) nanoparticles. Sherwan M. Mahdi Ismail

et al. have looked into how the Pinus Brutia (PB) tree extracts and various pH levels of the green manufacturing mixture (6 to 12) affect the characteristics of the ZnO NPs. At room temperature, one significant absorption peak at 275.3 nm was visible in the UV-Visible spectra of PB tree leaf extracts. The FESEM data obtained showed that the pH values significantly alter the morphology, orientation, shape, and dimensions of the green synthesized (GS) ZnO NPs, which are spherical in shape and range in size from (37.47 to 73.70 nm). Furthermore, the XRD results show that the synthesized GS ZnO NPs are GS ZnO with hexagonal and wurtzite crystal structure, with particle sizes along the (002) peak between the (16.9-24.15) nm range. Approximately (2.6-2.724) eV is the band-gap energy (Eg) that was determined. In comparison to ZnO NPs produced at various pH values, the final analysis revealed that the GS ZnO NPs produced at pH 8 displayed good quality and a significant improvement [61].

Zinc oxide (ZnO) nanoparticles have been developed environmentally friendly by M. MuthuKathija *et al*. using the reducing and capping agent of Pisonia Alba leaf extract. According to data spanning the ultraviolet to visible spectrum, the highest absorbence occurs at 375 nm, or an energy gap of 2.96 eV. The mean particle size was 48 nm, according to XRD analysis. Aloe-vera leaf-like and polydispersed NPs were developed, as seen in electron microscope images [62].

Vitex negundo plant extract was used to synthesize ZnO nanoparticles using zinc nitrate hexahydrate as a precursor. *S. aureus* and *E. coli* pathogens were resistant to biosynthesized zinc oxide nanoparticles' antibacterial activities [63]. Dobrucka and Dugaszewska [64] synthesized ZnO nanoparticles from trifolium pratense, and these particles were found to be hexagonal in shape and range in size from 60 to 70 nm. Using pulp extract from Lagenaria siceraria, Kalpana *et al.* [65] produced zinc oxide nanoparticles. The author also evaluated how well the biosynthesized ZnO nanoparticles worked against bacteria, arthritis, and dandruff. Zinc oxide nanoparticles were effectively produced from green tea leaf extract by Dhanemozhi *et al.* [66] to assess their capacitance behavior for supercapacitor applications. Inorganic nanoparticles known as ZnO nanoparticles are multifunctional and mostly used to treat urinary tract infections. To test zinc oxide nanoparticles against a pathogenic culture that was detached from the urine of a patient with a urinary tract infection, Santhoshkumar *et al.* [67] used Passiflora caerulea leaf extract. The study revealed that synthetic zinc oxide nanoparticles function as an antibacterial agent to treat urinary tract infections. Using Camellia sinensis extract, Nava *et al.* [68] discussed a low-cost, non-toxic green synthesis of zinc oxide nanoparticles. Siripireddy and Mandal [69] used Eucalyptus globulus to study zinc oxide nanoparticles' ability to act as a photocatalyst for the breakdown of several organic dyes, including methyl orange and methylene blue, as well as their antioxidant activity using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. The first demonstration of the green, unique, and environmentally friendly approach for producing monophase crystalline ZnO nanoparticles with a size span of around 15.8 nm was made by Thema *et al.* [70]. As a potent oxidizing/reducing agent, they used A. betulina extract. Zinc oxide nanoparticles were made stable and spherical using Aloe vera leaf extract with zinc nitrate. Investigations with the UV-Vis spectrophotometer, TEM, photoluminescence, FT-IR, XRD, and SEM were used to look at the different ZnO NP properties [38].

Biosynthesis of zinc oxide nanoparticles using microbes

Activated metal binding sites, intracellular metallic ion buildup, basic cell biochemistry, the transport of ionic metals across cells, defense mechanisms against poisonous metals, and metal oxide nucleation may all be included in the mechanisms used by microbes to produce nanoparticles71]]. Rhodococcus pyridinivorans NT2 was exploited to efficiently synthesize zinc oxide nanoparticles with a diameter of 100 to 120 nm and a high degree of stability 72]]. Zinc oxide nanoparticles produced by Serratia ureilytica (HM475278) have been described by Dhandapani *et al.* [73]. Zinc oxide nanoparticles have generated interest due to the several uses they have in the food sector. A novel technique for the production of zinc oxide nanoparticles utilizing the probiotic bacterium Lactobacillus plantarum VITES07 was described by Selvarajan and Mohanasrinivasan [74]. Using the actinobacterium Rhodococcus pyridinivorans NT2, Kundu *et al.* [72] produced zinc oxide nanoparticles from the zinc sulfate solution. The multifunctional finishing of textiles and in vitro anticancer drug delivery in the HT-29 colon carcinoma cell line were both investigated using the produced zinc oxide nanoparticles. In their research, Shamsuzzaman *et al.* [75] established a straightforward and

environmentally friendly method for producing ZnO nanoparticles by employing *Candida albicans* as a sealing and reductants. The quick and effective synthesis of steroidal pyrazoline was also accomplished by the author using the produced zinc oxide nanoparticles as a catalyst. Hussein *et al.* [71] cited *Bacillus cereus* as a bio-template agent for the production of zinc oxide nanoparticles with raspberry and plate-like forms by using a straightforward thermal breakdown of zinc acetate while maintaining the original pH of the reaction solutions. Using extracellularly generated *Aspergillus terreus* filtrate, Baskar *et al.* [76] created spherical zinc oxide nanoparticles with a range of 54.8 to 82.6 nm. The fungus's extracellular synthesis of nanoparticles is extremely favorable since it can be created in large quantities, is easily processed later, and is commercially viable [77] . Due to their improved metal bioaccumulation and tolerance properties, fungal strains are favored over bacterial ones [78]. The ZnO nanoparticles are produced from *Aspergillus fumigatus* mycelia [79]. The nanoparticles were created using *Candida albicans*, and their sizes, which ranged from 15 to 25 nm, were determined by TEM, XRD, and SEM study [75].

Applications of ZnO nanoparticles in biomedicine

Zinc oxide nanoparticles, a more contemporary type of less expensive, less hazardous nanomaterial, have drawn significant interest from the biomedical fields of anticancer, antioxidant, anti-inflammatory activity, antibacterial, and anti-diabetic, furthermore from bioimaging and medication administration [80]. This section will discuss some recent advancement in the usage of zinc oxide nanoparticles in biological applications. A greater understanding of molecular biology is now possible because of medical science's adoption of nanotechnology. The consequence, it may be feasible to develop new treatments for diseases that were difficult to target in the past because of size constraints [81]. For biomedical applications, the synthesis of bio-functional nanoparticles is crucial, and it lately attracted the interest of several research organizations that are growing exponentially in this field [82]. As various medical uses of zinc oxide nanoparticles were discussed in this study, a wide range of materials and chemical production processes currently being researched for biomedical applications. Natural and present in all living things, zinc served as vital metabolic purposes in people, animals, and plants. All living things require exposure to natural background amounts of zinc in the biosphere. Zinc oxide is widely utilized in cosmetic, pharmacological, and medicinal applications and is acknowledged as a good nutritional addition. Even while inhaling zinc oxide dust and fumes is generally thought to be safe, it must be avoided. To limit potential exposure scenarios, regulations have been put in place [83].

Anticancer activity

In recent years, cancer has been treated using surgery, radiation therapy, and chemotherapy. The uncontrolled malignant cell proliferation is characteristic of cancer. Although theoretically all these medications should be effective in eradicating cancer cells, they all have numerous negative side effects [30]. Compared to other nanoparticles, ZnO nanoparticles have an innate ability to exhibit specific cytotoxicity against malignant cells in an *in vitro* environment. They can also have their surfaces modified to exhibit more selective cytotoxicity. Without harming healthy cells, zinc oxide nanoparticles trigger the eradication of malignant cells [84].

Zinc oxide nanoparticles have been found to be toxic to both Gram-positive and Gram-negative bacteria and to have unfavorable effects on the health of primary human T cells, as per a study reported by Reddy *et al.* [85]. Adults need Zn(II) ions, thus living organisms are thought to be nontoxic to ZnO nanoparticles. Because of these advantages, zinc oxide nanoparticles are being studied for use in cancer therapy and as biodegradable and biocompatible nanoplatforms [29]. Zinc oxide nanoparticles exhibited anticancer activity by increasing ROS generation and apoptosis. Moreover, zinc oxide nanoparticles electrostatic properties, which have been utilized for anticancer activity, are a useful property. Zinc oxide nanoparticles exhibited distinctive surface charge behavior due to the hydroxyl groups that are neutral that have been chemisorbed onto their surfaces. Protons (H^+) flow away from the surface of a particle in an aqueous solution with a high pH, causing atoms of oxygen that are only loosely bound to have a negative charge on their surface (ZnO). A positive charge zinc hydroxide ($ZnOH_2^+$) is produced on the particle surface at lower pH levels because of protons from the surrounding environment being transferred there [86]. Zinc oxide nanoparticles exhibited a significant positive surface charge under physiological conditions and

an isoelectric point of 6.4-7.5 [86]. As opposed to that, the membrane potentials of cancer cells are notably negative and have a number of anionic phospholipids (phosphatidylserine) on the surface of their membranes [87]. Interactions between electrostatic charges that boost cellular uptake, cytotoxicity and phagocytosis are what cause cancer cells to react with positive charge zinc oxide nanoparticles [86]. Several investigations have found that while these nanoparticles are harmless to mature human dermal fibroblasts [88] and endothelial cells in vessels [89], they are detrimental to metastatic tumor cells. Simultaneously promoting neural stem cell apoptosis (programmed cell death). Due to its high biocompatibility, ability to target cancer, ease of surface functionalization, and ability to distribute drugs, nanomaterial-based nanomedicine has recently demonstrated the ability to address these undesirable effects. Before zinc oxide nanoparticles may be employed in medicine, several obstacles need to be resolved, including the lack of acceptable biocompatible dispersion methods and the best knowledge of the mechanism of their unique cytotoxic impact [90].

The catabolic process of autophagy is strictly controlled and is brought by a variety of stimuli, including reactive oxygen species (ROS), destroyed organelles, protein aggregation and anticancer medications. Apoptosis in cancer cells can be brought on by excessive cell damage by expanding autophagy and causing cellular self-consumption, resulting in cell destruction [91]. Hence, autophagy plays a significant role in nanoparticle-induced cytotoxicity by increasing cell viability and activating death pathways in cancer cells. Zinc oxide NPs were synthesized by Baraa Y. Hussein *et al*. using a reduction agent derived from aqueous grape extract (Vitis vinifera). When tested against the Gram-negative bacterial strain *Klebsiella pneumoniae* and the Gram-positive bacterial strain *Staphylococcus aureus*, the produced ZnO NPs showed a considerable inhibitory efficacy against pathogenic bacterial strains. Additionally, MCF-7 and AMGM5 human cancer cell lines exposed to ZnO nanoparticles demonstrated considerable cytotoxicity. Therefore, Hussein *et al.* study showed how ZnO NPs could be used as a medication against bacteria and cancer [92].

Senthilkumar Chandrasekaran *et al*. developed ZnO NPs in two separate ways chemically and using plant leaves and then examined the effectiveness of their anticancer, anti-diabetic, and antibacterial capabilities. Due to the presence of alkaloids, sample GS-ZnO NPSs demonstrated the highest efficiency of a-amylase inhibition (84.37%) and the lowest efficacy of CS-ZnO NPs (83.85%). Furthermore, GS-ZnO NPs had a potent cytotoxic effect on the MCF7 cell line. The efficiency of CS-ZnO NPs against the following microorganisms, including *Staphylococcus aureus, Bacillus subtilis, E. coli, S. typhi, Candida albicans, and Aspergillus niger*, was only 50% when compared to typical antibacterial activity. While GS-ZnO NPs had more anti-microbial efficacy against *Bacillus subtilis and S. typhi* than the standard by about 3 times or 1.5 times, respectively, GS-ZnO NPSs shown greater anti-microbial efficacy against other microorganisms by around 100% [93].

Using zinc oxide nanoparticles as a cancer drug delivery

The potential for safer and more effective cancer treatments is greatly increased by the incorporation of nanoparticles in formulated drugs. Reducing the overall number of medications used is possible by using nanoparticle-based drug delivery and also, eliminating unfavorable side effects by targeting certain regions of cancer cells [86]. Zinc oxide nanoparticles are desirable, when compared to other nanomaterials, because they are less poisonous and more biodegradable. There is a lot of interest in the use of zinc oxide nanoparticles in the administration of cancer medications. Loading drugs such doxorubicin, paclitaxel, curcumin, and baicalin onto ZnO nanoparticles can show solubility, superior toxicity, and distribution into cancer cells compared to using the drugs alone [94]. Earlier studies have revealed that zinc oxide nanoparticles› cytotoxicity is influenced by ROS and autophagy. On the other hand, the mechanisms that control ROS and autophagy have not yet been identified. In lung epithelial cells, Zhang *et al.* [41] exploration the mechanics that regulate autophagy and the connection between autophagy and ROS with the use of zinc oxide nanoparticles.

Zinc oxide NPs were synthesized by Madiha Batool *et al.* utilizing Aloe barbadensis leaf extract as a stabilizing and capping agent. Doxorubicin (DOX) and gemcitabine (GEM) were used to measure the drug loading capacity (LC) and loading efficiency (LE) of unstabilized and PEGylated ZnO-NPs. On ZnO-NPs, DOX showed superior LE 65% (650 mg/g) and greater

LC 32% (320 mg/g) than GEM, which had LE 30.5% (30 mg/g) and LC 16.25% (162 mg/g). Similar results were found for PEG-ZnO-NPs, where DOX had increased LE 68% (680 mg/g) and LC 35% (350 mg/g), in contrast to GEM, which had LE and LC values of 35% (350 mg/g) and 19% (190 mg/g), respectively. So, using the MTT (3-(4,5-dimethylthiazol-2-Yl)-2,5-diphenyltetrazolium bromide) assay, DOX was chosen to encapsulate nanoparticles alongside the untreated nanoparticles to test their in vitro antiproliferative potential against the triple-negative breast cancer (TNBC) cell line (MDA-MB-231) [95].

Rajagopal Gomathi *et al.* loaded doxorubicin into green manufactured zinc oxide nanoparticles made using the solgel technique. Drug loading was done under various pH (3.0, 6.0, 8.2, and 10.0) settings. Based on the findings of the UV and SEM analysis, pH 6.0 was shown to be the ideal condition. Additionally, using the MTT colorimetric cell viability assay, the in vitro cytotoxicity of DOX, ZnO, and ZnO-DOX against HeLa cells was investigated. Zinc oxide-DOX cells were 99.4% inhibited at a dosage of 100 g/mL. Thus, the findings offer convincing support for green biosynthesized ZnO, which may work well as a potential nano-drug carrier for the targeted drug delivery system [96].

Cytotoxic effect of zinc oxide nanoparticles on cancer cells

Without having any cytotoxic effects on healthy cells, zinc oxide nanoparticles cause the demise of malignant cells [63, 64]. Before putting zinc oxide nanoparticles to use in medicine, there are a number of issues that need to be fixed, including the lack of suitable biocompatible dispersion techniques and the need for a much deeper comprehension of the mechanism underlying their selective cytotoxic effect [97]. There hasn't been much investigation on the cytotoxicity of ZnO nanoparticles on mammalian cells, and there isn't consensus among specialists regarding the significance of published results. According to a study, zinc oxide nanoparticles have detrimental impact on primary human T cells' survival at concentrations that are toxic to both Gram-negative and Gram-positive microorganisms [65]. Numerous publications claim, these nanoparticles are not hazardous to human dermal fibroblasts grown in culture, but they are poisonous to cells that can spread cancer and to vascular endothelial cells and induce apoptosis in brain stem cells [67]. The size of nanoparticles has also been linked to potential effects on cell survival. In *Staphylococcus aureus*, Jones et al. found that zinc oxide nanoparticles with a size of eight nm were more hazardous than those with a size of 50–70 nm [68]. Hanley *et al.* have recently found that nanoparticle size and toxicity in class cells, such as nanoparticle size and the production of reactive oxygen species, are inversely related [83], whereas Deng *et al.* have demonstrated that zinc oxide nanoparticles have a toxic effect on neural stem cells in a dose-dependent manner without regard to particle size [69].

Focusing on Functionalization

Beyond localization and city, targeted nanoparticles (NPs) offer other therapeutic benefits, including multidrug conjugation, high payload, simple discharge kinetics adjustment, selectiveness localization, and evading multidrug resistance mechanisms [98].Conducive has described a variety of functionalization techniques for nanoparticle modification to improve the selectiveness and targeted actions against cancer cells. Zinc oxide nanoparticles selectivity and durability against some cancer cells were further enhanced by surface modification. The research focuses on surface modification of zinc oxide nanoparticles using a diversity of biological compounds, including proteins, folic acid, nucleic acids, peptides, hyaluronan, and others [43, 50]. The biocompatible coating had no effect on the anticancer activity of zinc oxide nanoparticles, but it did improve their capacity to specifically attack cancer cells and their defense against normal cells.

Anti-diabetic activity

Since zinc is critical for the storage, creation, and secretion of insulin, zinc oxide nanoparticles have been studied for their antidiabetic properties. Increased levels of insulin, glucose elimination, and zinc status were observed to indicate zinc oxide nanoparticles had superior anti-diabetic efficacy versus $ZnSO_4$ [99]. Wahba *et al.* [100] reported that improvements in ultrastructure, structural quality, and normalization of serum insulin and blood sugar levels biochemically were evidence of the efficacy of zinc oxide nanoparticles in the treatment of diabetes-stimulated pancreatic disease. Red sandalwood and vildagliptin, two diabetes medications, were combined with zinc oxide nanoparticles in subsequent experiments to boost their effectiveness [101]. Both the pancreatic enzyme

amylase and the colonic enzyme -glucosidase break down oligosaccharides and disaccharides to produce monosaccharide (glucose) [102]. A lack of insulin secretion or activity is the cause of metabolic condition diabetes. Its hallmarks include ineffective carbohydrate metabolism and persistent hyperglycemia [103]. Because insulin doesn't work well, Diabetic patients' blood glucose levels continue to climb. Blood glucose levels can be managed via glucosidase and amylase inhibition. The amylase and glucosidase enzymes can currently be inhibited with a large variety of medications; however, these medications also come with some disadvantages [104]. Amylase and glucosidase activity is inhibited by Ci- zinc oxide nanoparticles. Amylase inhibition percentages varied from 20% (20 g/ml) to 74% (100 g/ml), whereas -glucosidase inhibition percentages varied from 36% (20 g/ml) to 82 percent (100 g/ml). The rate of inhibition for glucosidase was higher than that of amylase [105].

More than 400 million individuals have diabetes in the world in 2014, which is a serious public health problem, according to the World Health Organization (WHO) [99]. Diabetes mellitus is a metabolic illness brought on by the body's failure to produce enough insulin or by the ineffective utilization of the insulin that is produced [100]. Human fluids and tissues contain significant amounts of the trace metal zinc. It is widely known that zinc plays a significant role in the release of insulin from pancreatic cells and in maintaining the structural integrity of insulin. Additionally, it takes involvement in the storage, production and secretion of insulin [106]. Consequently, zinc oxide nanoparticles have been developed as an innovative technique for zinc administration, and their antidiabetic effects have been studied. In combination with ZnO nanoparticles, Kitture *et al.* used red sandalwood natural extract (RSW) as a powerful antidiabetic drug. With the aid of a murine pancreatic and small intestine extract inhibition experiment, the antidiabetic efficacy was evaluated [102]. Results indicated that ZnO-RSW compound was more efficient than each of both components (RSW and zinc oxide nanoparticles) against crude murine pancreatic glucosidase and had a slightly greater percentage of inhibition (20%) against pig pancreatic α-amylase. While the unprocessed zinc oxide nanoparticles and RSW demonstrated 21,48 and 5,90%, respectively, of α-glucosidase inhibition, 61.93 percent was shown by the conjugate ZnO-RSW.

In a 2015 study, Nazarizadeh and Asri-Rezaie investigated the antioxidant activity of zinc sulphate ($ZnSO_4$) and zinc oxide nanoparticles in diabetic rats. In comparison to $ZnSO_4$ (30 mg/kg), small zinc oxide nanoparticles were found to have a substantially stronger antidiabetic effect at higher doses (3 and 10 mg/kg). It was shown by a notable drop in blood sugar, an increase in insulin levels, and a dose- and time-dependent improvement in serum zinc status. Nevertheless, the altered erythrocyte antioxidant enzyme activities, elevated malondialdehyde (MDA) production, and markedly reduced serum total antioxidant capacity all indicated severely induced oxidative stress, particularly at higher dosages [100]. By controlling C-reactive protein (CRP) and cytokines like interleukins, which are associated with the emergence of cardiovascular illnesses, hyperglycemia can directly exacerbate an inflammatory condition. To lessen the effects of diabetes problems, Hussein *et al.* created zinc oxide nanoparticles using hydroxyethyl cellulose as a stabilizing agent [103]. Asymmetric dimethylarginine (ADMA), rapid blood sugar, malondialdehyde (MDA), and the inflammatory markers interleukin-1 (IL-1) and CRP were all shown to be considerably reduced in diabetic rats treated with zinc oxide nanoparticles. The therapy also resulted in elevated levels of nitric oxide (NO) and PON-1, a blood antioxidant enzyme. The medically useful leaf extract of Tectona Grandis, Abutilon Indicium, was used by K. Muhil Eswari *et al*. to synthesize ZnO nanoparticles. With an average crystalline size of 17 nm for ZnO nanoparticles mediated by Tectona Grandis and 22 nm for Abutilon Indicum, respectively, the XRD pattern showed the effective synthesis of wurtzite ZnO nanoparticles. The results of the optical experiments revealed substantial absorption bands in the UV region of 350 nm and band gap values of 3.0 eV and 3.1 eV. By using Bovine Albumin Serum (BSA) denaturation and -amylase Inhibition Techniques, the bio-medical activities of the produced ZnO nanoparticles, such as anti-inflammatory and anti-diabetic analyses, were evaluated. Against -amylase and bovine serum albumin, respectively, the maximum inhibition percentages of 95.42% and 94.82% are found. Additionally, the MTT experiment used to test the *in-vitro* cytotoxicity of ZnO nanoparticles showed that MCF-7 breast cancer cell lines had lower viability. All reports of zinc oxide nanoparticles for the treatment of diabetes, and the available

data revealed that zinc oxide nanoparticles would be a potential treatment for both the illness and its side effects.

Antibacterial Activity

Due to its amazing qualities, such as a significant amount of surface area and the capacity to death a variety of diseases, zinc oxide nanoparticles are a potential antibacterial substance. Zinc oxide nanoparticles antibacterial activity, however, was just recently found. Zinc oxide nanoparticles are recognized as a potent medication in the creation of microscale and nanoscale systems for medicinal purposes. Even though zinc oxide nanoparticles seem to have more medical therapeutic potential than microparticles, the precise mechanisms of the drug›s action are still unknown. Gram-positive and Gram-negative bacteria are both susceptible to the germicidal effects of zinc oxide nanoparticles [49]. When confronted by spores that can resist high pressure and temperatures, they also have antibacterial effectiveness. Even if crystalline structure and particle shape barely matter, ZnO NP concentration and size determine how they behave pharmacologically. Hence, it is shown that the therapeutic pharmacological activity increases with nanoparticle extent and concentration. In the whole, the mechanism of zinc oxide nanoparticles medicinal pharmacological activity is still unknown. Others theorized that particle attachment to the surface of the microbe owing to fixed pressures may also be a factor. While some studies asserted that the main issue with medical therapy is the generation of hydrogen peroxide, others maintained that this is not the case .[٩٠] With higher particle doses, nanoparticle potency will rise, treatment time, and production technique. Additionally, the greatly enhanced antibacterial activity indicated by these studies is unquestionably a result of the particle size variability and surface area to volume ratio of green Zinc oxide nanoparticles. Untrained zinc oxide nanoparticles could be used well in agricultural applications, food safety applications, and medicinal difficulties in the future, according to the researchers [107]. The most often utilized model species to study zinc oxide nanoparticles antibacterial activity right now are *Escherichia coli* (*E. coli*), *Vibrio cholerae* (*V. cholerae*), and other Gram-negative bacteria [108], as well as Gram-positive bacteria like *Staphylococcus aureus* (*S. aureus*) [47]. *Proteus vulgaris* (*P. vulgaris*), *Pseudomonas aeruginosa* (*P. aeruginosa*) [45], and other Gram-positive bacteria including *Enterococcus faecalis* (*E. faecalis*) [53] and *Bacillus subtilis* (*B. subtilis*) [54] were also included in research. Zinc oxide nanoparticles have antibacterial activity against *E. coli*, according to Jiang *et al.* [109]. Zinc oxide nanoparticles were synthesized by Tu Uyen Doan Thi *et al.* using orange fruit peel extract, and they demonstrated that after 8 hours of incubation and at a concentration of 0.025 mg mL^{-1}, the ZnO NPs had strong antibacterial activity against *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) [56]. Scavenging free radicals such mannitol, vitamin E, and glutathione could prevent zinc oxide nanoparticles from killing bacteria, suggesting that ROS production was necessary for zinc oxide nanoparticles to have antibacterial effects. Zinc oxide nanoparticles with a mean range size of 30 nm have been found to kill cells by directly contacting the phospholipid bilayer of the membrane and compromising the integrity of the membrane. Zn(II) ions produced from ZnO NP suspensions did not, however, seem to have an antibacterial effect as described by Reddy *et al.* [29]. Zinc oxide nanoparticles with a diameter of 13 nm were created and tested for their antibacterial activity against *E. coli* and *S. aureus* germs. The results showed that zinc oxide nanoparticles completely inhibited the growth of *E. coli* at doses of about 3.4 mM, but stopped completely the development of S. aureus at doses of less than 1 mM [85].

People in underdeveloped countries are more likely to contract the deadly diarrheal disease cholera, which is caused by the Gram-negative bacterium *V. cholera*, which intestines it affects [٨١]. In order to create a nanomedicine to treat cholera, two cholera bacteria biotypes, Vibrio cholerae, were studied by Sarwar *et al.* [82] in relation to the impacts of zinc oxide nanoparticles (classical and El Tor). It was demonstrated that zinc oxide nanoparticles inhibited the El Tor (N16961) biotype of V. cholera's rapid growth, which was related mainly to the overproduction of ROS's. These effects would damage bacterial membranes, increase permeabilization, and dramatically change their structure. Zinc oxide nanoparticles demonstrate antibacterial activity in cholera toxin (CT) mice models. The capacity of zinc oxide nanoparticles to interfere with CT's attachment to the GM1 gangliosides receptor and interact with CT by causing a progressive collapse of the secondary CT structure has been discovered [83]. Zinc oxide nanoparticles' precise antibacterial mechanism is still a mystery. So, a thorough knowledge of it has both theoretical and

practical significance. Further research on zinc oxide nanoparticles as antibacterial agents for mouthwashes, creams, and lotions is something we anticipate. In biomedical applications, it can also be coated on a number of substrates to prevent germ from adhering to them, spreading through them, and reproducing. The antibacterial activity of zinc oxide nanoparticles is also influenced by their ability to induce oxidative stress. Respiratory enzymes' ability to operate is constrained by interactions with Zn(I) ions made by ZnO by their thiol group. It has been shown that zinc oxide nanoparticles have an impact on cell membranes and cause the production of ROS. As a result of bacteria absorbing Zn(I) from zinc oxide nanoparticles, respiratory enzyme activity is inhibited, ROS and free radicals are produced, and oxidative stress is brought on. ROS permanently harm bacterial membranes, DNA, and mitochondria, which causes bacterial cell death 110]] . Jalal and Ghasemi [111] used zinc oxide nanoparticles to study the efficacy of the traditional antibiotic's ceftazidime and ciprofloxacin as well as the mechanisms of action against resistant *Acinetobacter baumannii*, an opportunistic pathogen that causes pneumonia and meningitis. The results showed that the presence of a sub - inhibitory concentration of zinc oxide nanoparticles increased the antimicrobial activities of both drugs. Antibiotic absorption was increased and rod-shaped bacteria were changed into cocci when zinc oxide nanoparticles were used in conjunction with antibiotics. According to these findings, bacterial infections can be treated by combining zinc oxide nanoparticles and antibiotics. Moreover, it has been discovered that zinc oxide nanoparticles enhance the antibacterial activity of the photosensitizer crystal violet (CV) [112]. Microbes of both the Gram-positive and Gram-negative types respond to zinc oxide nanoparticles by exhibiting antibacterial activity [97]. Zhang *et al.* [113] used the Surface Enhanced Raman Spectroscopy (SERS) method to examine the dosage- and moment-dependent phenotypic bacterial response to zinc oxide nanoparticles. Their research showed profiles of spectral change that were both understandable and useful. Smaller dose limits showed significant variations rather than larger dose limits, indicating that zinc oxide nanoparticles bioavailability decreased with increasing dosages. Rapid activity was established within 0.5 hours, and lesser dosages and extended exposure times exhibited effects comparable to those of substantial dosages.

Anti-microbial effect of zinc oxide nanoparticles

To combat drug resistance to many medications; next-generation nano-antibiotics against dangerous bacteria have been developed using zinc oxide nanoparticles[114] These nanoparticles are distinctive in terms of their size, crystalline structure, porosity, morphology, and composition 63]] . These properties give zinc oxide nanoparticles broad antibacterial activity against a range of pathogens, such as the M13 bacteriophage, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* [67]. They can be combined with antibiotics and anti-inflammatory drugs in both non-clinical and clinical settings to boost antibacterial action against pathogenic microorganisms without promoting antibiotic resistance67,68]]. Despite the lack of clarity regarding the precise mechanism of medicinal action, in formulations at the micro- and nanoscale levels, ZnO is being investigated as a pharmacological agent. According to certain claims, the concept of ROS created on particle surfaces, zinc ion discharge, membrane dysfunction, and nanoparticle acquisition area unit are the main causes of cell ballooning.

Processing zinc oxide nanoparticles at high temperatures has a significant impact on their therapeutic action, in contrast to processing them at lower temperatures, which has less of an impact [7]. Medical ablation procedures are being studied in conjunction with zinc oxide nanoparticles. Nanoparticles can even be imaged to confirm the validity of medical advice. They will develop anti-cancer drugs that act synergistically in the presence of heat. contribute to neoplasm ablation having a larger thermal effect as well. The capacity to develop nanoparticles with the suitable composition and properties to increase the ablation property should be made possible by understanding the molecular mechanism underlying tumor-mediated nanoparticle ablation, claim research [71]. Based on their distinctive physicochemical properties of (a) Zn(II) ion release, (b) adsorption, (c) ROS generation, (d) the intracellular responses in microorganisms, (e) lipid peroxidation, (f) DNA replication disruption, and (g) DNA break [73], ZnO materials› mechanisms of antimicrobial action have been linked to specific interactions. Zn(II) ions synthesized by zinc oxide nanoparticles/ MPs create an antibacterial response in microbes because they interfere with metabolic processes and disrupt enzyme systems [76]. Furthermore, when exposed to UV and visible light, zinc oxide

nanoparticles/MPs operate as photocatalysts to create ROS and can adsorb particles to the bio-membrane through a charge-charge interaction 79 ,78]]. Zinc oxide nanoparticles and MPs engage with microorganisms that have negatively charged cell walls or bio-membrane and positively charged surfaces. After adsorption, the particles are absorbed by the bacteria, whereupon a rupture of the membrane or cell wall results in the loss of cell integrity. They also function as mediators of lipid peroxidation-induced oxidative stress, which causes DNA damage. Zinc oxide nanoparticles/MPs differ in their vulnerability to harmful germs based on their fundamental modes of action and physical characteristics including shape, particle size, and porosity [115, 116]. Zinc oxide nanoparticles and very infrequently MPs show improved antibacterial activity even against dangerous viruses. Additionally, they have widespread antimicrobial effects when combined with other antibiotic drugs, which can be tailored for different treatment modalities and utilized to make them more appealing as platforms for commercial and clinical translation. Other biomaterials, metal doping or metal oxide NPs/MPs [117].

Antifungal activity

In addition to being effective against bacteria, zinc oxide nanoparticles are also effective against fungi. *Sclerrotium rolfii* and *Alternaria saloni*, two plant pathogen strains, were harmful to zinc oxide nanoparticles produced from M. oleifera as described by Surendra *et al.* [118] Gunalan *et al.'s* [119] examination into from zinc oxide nanoparticles' antifungal efficacy against several fungal strains discovered that they were detrimental to plants and food pathogens in the following order: *Aspergillus nidulans* > *Trichoderma harzianum* > *Rhizopus stolonifera* > *Aspergillus flavus*. Therefore, the researchers suggested that the formed zinc oxide nanoparticles might be useful for the food and agricultural industries. According to Lipovsky *et al.*, zinc oxide nanoparticles affect *Candida albicans* viability in a concentration-dependent manner [120]. *C. albicans'* vitality was drastically decreased by zinc oxide nanoparticles (0.1 mg/ml). When combined with zinc oxide nanoparticles, visible light increased yeast cell death more frequently.

ZnO NPs were synthesized by R Perveen *et al*. utilizing aqueous extracts of vegetable seeds from Brassicaceae plants, including red, white, turnip, sarson, and cauliflower. Zones of inhibition for the ZnO NPs, which showed potential antibacterial action, ranged from 10 to 20 mm, compared to 25 mm for Streptomycin (the gold standard antibiotic). In order to create ZnO as active antibacterial agents, red radish, white radish, turnip, sarson, and cauliflower may be employed [121].

Anti-inflammatory activity

Inflammation is a complex biological response of the body tissues to stimuli that could be harmful, such as bacteria, damaged cells, or irritants. The biological activities of zinc ions and the creation of nanoparticles have made people aware of the zinc oxide nanoparticles' anti-inflammatory effects. The weakening of the skin-barrier functions is a hallmark of the chronic inflammatory skin condition known as atopic dermatitis (AD) [122]. This condition is also characterized by a complicated interplay between hereditary and environmental variables. The longest and closest to the skin materials are textiles. Studies conducted in vitro and in vivo by Wiegand [123] looked at the role of ZnO functionalized textile fibers in the control of oxidative stress in AD. The study discovered that when AD patients wore the ZnO textiles overnight on 3 consecutive days, there was a noticeable improvement in both pruritis and varying levels of sleep quality. The strong antibacterial and antioxidant properties of ZnO textiles could be to blame for this. Ilves et al. [125] investigated if different-sized zinc oxide nanoparticles may affect allergic skin and penetrate wounds in the mouse AD model. Their study adequately shown that bulk-sized ZnO (bZnO) remained at the skin's surface layers in both allergic and wounded skin, but that only nano-sized ZnO (nZnO) could reach the skin's deeper layers in allergic skin. Nano-sized zinc oxide dramatically reduced pro-inflammatory cytokines in the animal model of AD, exerting greater anti-inflammatory effects than bZnO. (IL-10, IL-13, IFN-, and Th2 cytokines). These results showed that in AD models, small zinc oxide nanoparticles significantly reduced skin inflammation.

Zinc oxide nanoparticles' anti-inflammatory properties have been demonstrated to be highly beneficial for treating a variety of inflammatory illnesses, not just atopic dermatitis. Given that zinc oxide nanoparticles are known to have stronger anti-inflammatory activity, Nagajyothi *et al.* presented a straightforward, affordable, and environmentally friendly zinc oxide nanoparticles utilizing P. tenuifolia root extract, and the anti-

inflammatory capabilities of LPS-stimulated RAW 264.7 macrophages were evaluated [84]. By dose-dependently reducing NO generation as well as the associated protein expressions of iNOS, COX-2, IL-1, IL-6, and TNF-, zinc oxide nanoparticles revealed impressive anti-inflammatory efficacy. By using an aqueous leaf extract of *Pelargonium odoratissimum*, which serves as a reducing agent, Ahmed S. Abdelbaky *et al*. have synthesized ZnO nanoparticles. Human red blood cells (HRBC) membrane stabilization method (MSM) *in vitro* models, which include hypotonicity-induced hemolysis, were used to assess the anti-inflammatory effects of both ZnO NPs and the aqueous leaf extract of *P. odoratissimum*. When ZnO NPs were compared to regular indomethacin at a concentration of 1000 g mL^{-1}, a maximum membrane stabilization of 95.6% was discovered [124]. In light of this, zinc oxide nanoparticles may also be used to treat inflammation. Looked at the efficacy of bulk and nano-ZnO. Based on ZnO's ability to reduce inflammation, researchers discovered that only nano-ZnO may penetrate allergenic skin's thickest layers. Furthermore, nano-ZnO reduced localized skin irritability and aided the body's production of IgE antibodies. The authors propose that this result is a result of non-specific processes induced by freed Zn(II) reducing IgE production by B cells as described by Ilves *et al.* [125]

Treatment of a variety of skin disorders

Medications to treat a variety of skin issues frequently contain zinc oxide, including diaper rash powder, barrier creams, antimicrobial ointments, hemimorphite cream, and anti-dandruff shampoos. It is also a part of a tape called "zinc chemical compound tape," which is used by athletes as a bandage to safeguard soft tissue when working out. Sunburn and other UV-related skin diseases can be prevented by including zinc oxide nanoparticles into creams, ointments, and lotions. Due to its wide-spectrum UV-A (320-400 nm) and UV-B (280-320 nm) reflectivity and complete photostabilty, the Bureau has certified it for use as sunscreen [126].

Previous research has shown that ZnO-NPs cause the type I collagen in skin tissue to be downregulated. The findings demonstrated the protective effects of ZnO-NPs cream against lead oxide-induced oxidative damage and allergic dermatitis of the skin at low (1%) and high (6%) concentrations. This might be connected to ZnO-NPs' ability to reduce inflammation and act as antioxidants. [127] According to Wang et al.'s study, frequent and continuous exposure to ZnO NPs under the circumstances of epidermal barrier malfunction carries a risk of developing melanoma. The obtained results showed that, in a mouse model of epidermal barrier dysfunction, topical exposure to ZnO NPs causes these particles to penetrate the stratum basale of the epidermis, leading to the development of melanoma-like lesions on the skin. Additionally, both *in vivo* and *in vitro*, persistent exposure to ZnO NPs caused an anti-apoptotic effect in melanocytes through activating NF-κB pathways through oxidative stress [128].

Drug delivery

One of the many uses for nanotechnology is medication delivery, which has been shown to be effective in treating a number of disorders, including cancer [18]. One of the most important systems for the delivery of pharmaceuticals (NPs) is the use of nanoparticles. Numerous researchers have employed zinc oxide nanoparticles to deliver medication for a variety of ailments [18]. In a work to specifically target doxorubicin in HeLa cells, Yuan *et al.* [122] employed ZnO quantum dots as a drug delivery method. They covered zinc oxide nanoparticles with chitosan to increase the nanomaterial's stability. According to their research, doxorubicin may be successfully administered to cancer cells by means of drug delivery technology [122]. Another important element of their employment is the use of NPs as gene delivery systems for various cells, in particular malignant cells [2]. This approach to gene transfer has several benefits. For instance, plasmid-containing genes could be efficiently and safely transported to the recipient tissues by being placed on the surface of nanoparticles (NPs) [18].

Bio-imaging

This approach to gene dispersal has several benefits. For instance, genes synthesized on the surface of NPs that are encoded by plasmids may ensure that genes are transferred to the destination tissues safely and effectively [18, 129].. Zinc Oxide nanostructures have been discovered recently, including NPs, nanotubes, nanorods, and nano rings. For usage as bio-imaging agents, zinc oxide nanoparticles are being researched [129]. This trait has diverse biological and clinical applications and can be applied to varying degrees. For instance, luminescent zinc oxide nanoparticles, often referred to as ZnO QDs, may have advantageous photophysical characteristics

[129]. In general, ZnO is regarded as a secure chemical. In addition to being a food additive in food packaging, ZnO has been employed in sunscreen applications. As a result, the glowing properties of Zinc oxide nanoparticles can be used in a variety of natural and therapeutic applications [129].

Fluorescence imaging is widely used in preclinical research because it is practical and affordable [103]. There are several reports from earlier studies on the use of ZnO nanoparticles because they are necessary for cellular imaging, near-UV emission and excitonic blue, which has green luminescence connected to O_2 vacancies [119], and other processes. Cancer cell imaging with the least degree of harm was accomplished using transferrin-conjugated green-fluorescent zinc oxide nanoparticles [125]. By tampering with the appropriate elements, ZnO nanomaterial's optical characteristics could be changed. Zinc oxide nanoparticles were allegedly contaminated with different cations, such as Co, Cu, or Ni, stabilized in aqueous colloidal solutions, and then used in diverse cells for cellular imaging experiments [126]. It is possible for these tiny ZnO nanoparticles to enter the cell nucleus. Optical properties and biocompatibility of heterostructural ZnO/Au nanocomposites are made and investigated [122]. Zinc oxide nanorods' tips or the surfaces of the nanorods can both produce Au NCs. In the most recent study, antiepidermal growth factor receptor antibody attached ZnO nanorods were utilized to image cancer cells *in vitro* [123]. Due to their multiple appealing optical features, QDs are widely considered nanoparticles for optical imaging [130]. When used for *in vitro* cell imaging, ZnO QDs were found to be positioned in the cytoplasm and to demonstrate stable luminescence under UV light in the lack of necessary cytotoxicity. In other studies, using mice that received intravenous and intradermal injections, the same QDs were examined [37]. Every imaging method has advantages and disadvantages of its own [131]. Nanomaterials can be functionalized to be observable using a variety of imaging modalities, which has synergistic benefits. Nanomaterials, as opposed to small molecules, are better suited for multimodality imaging due to their larger surface areas, which provide more sites for functionalization and facilitate the tailoring of them for multimodal detection. In one study, Gd-doped ZnO QDs were created for optical and magnetic resonance imaging (MRI) with diameters less than 6 nm [132]. In a different work, for potential cancer imaging and treatment, Singh described Fe_3O_4-ZnO core-shell magnetic QDs. Single-photon emission computed tomography (SPECT) and radionuclide-based imaging methods, such as PET [37], are more frequently utilized in clinical settings than optical imaging. The tissue penetration of PET and SPECT techniques is not only limitless but also extremely sensitive and quantitative [131].

Researchers have recently discovered that ZnO nanoparticles come in a variety of forms that can be used as bioimaging materials. Hyperbranched polymers were used by G. Lei *et al.* [133] to manufacture the amphibious ZnO Quantum dots with blue fluorescence and explore their use for bioimaging. Zinc Oxide nanoparticles' surfaces are easily modifiable; they are stable in aqueous solutions, and after carefully making the change, their quantum dots (QDs) increase by about 30%. The scientists conclude by stating that water-soluble ZnO with hyper-branched polyethylenimine compounds performs the best for bioimaging applications. Using conventional fluorescence microscopy techniques, Masar *et al.* [134] studied pure n-type ZnO nanoparticles for bioimaging applications. In most cases, UV excitation sources are needed for nanoparticles to create emissions. Here, the scientists show that by closing the energy gap, a 405 nm laser may sufficiently excite the nanoparticles to allow for the detection of their emissions during confocal microscopy live-cell imaging investigations. The study establishes the groundwork for using these nanoparticles for various bioimaging applications. Through the use of fluorescence-based imaging techniques, it enables researchers to test the interactions of pure n-type ZnO nanoparticles with human cells. Their evolving synthesis method, which is being used to regulate certain flaws in pure n-type ZnO nanoparticles for bioimaging applications [135].

Zinc oxide nanomaterial-based biosensors

In the food business, healthcare, environmental monitoring and biological or chemical analysis, biosensors are widely used. When grouped according to the principles of detection, examples of biosensors include electrochemical, photometric, piezoelectric, and calorimetric devices [136]. Due to their unique properties, nanomaterials are gaining more and more attention, whether alone or in conjunction with biologically active chemicals [19]. For the

creation of high-performance biosensors, they can serve as a solid basis. The greater surface area of nanomaterials, for instance, might be used to immobilize a variety of biomolecules, including antibodies, enzymes, and other proteins. Additionally, it might be made easier for an electron to transfer directly from the electrodes to the active areas of the biomolecules. In addition to their semiconducting properties, ZnO nanomaterials have a number of other desirable characteristics, including high isoelectric point, strong adsorption capacity, biosensing, and high catalytic efficiency (IEP; 9.5), which are suitable for the electrostatic adsorption of specific proteins, such as enzymes and antibodies, which have lower IEPs [137]. Additionally, nanomaterials with stronger electron transfer capabilities, larger surface areas, and better biocompatibility or stability are more advantageous for application in biosensors [138]. The most popular ZnO-based biosensors can identify a variety of small-molecule analytes, including cholesterol, glucose, H_2O_2, phenol, urea, and many more compounds. There are numerous biosensors available as well for identifying different substances and certain chemical or physical properties, such as pH [139].

Soner DNMEZ [140] developed an amperometric glucose biosensor based on environmentally friendly zinc oxide (ZnO) nanoparticles using the root of the zingiber officinale. Through cross-linking with glutaraldehyde, glucose oxidase (GOx) was immobilized onto the carbon paste electrode (CPE) modified with ZnO. The biosensor that was created (GOx-ZnO/CPE) demonstrated good electrocatalytic performance in the measurement of glucose. Additionally, the biosensor demonstrated a low detection limit (14.7 uM), a quick response (less than 1 second), high sensitivity (15.98 A mM^{-1} cm^{-2}) and increased biological affinity (the Michaelis-Menten constant was estimated to be 0.99 mM). Additionally, the constructed biosensor showed good resistance to interference by uric and ascorbic acids.

Nano-toxicological effects of zinc oxide nanoparticles

Zinc oxide, which is normally thought of as a chemical that is insoluble in water, was shown to have dangerous properties by releasing Zn-ions in the case of ZnO nanoparticles. The size, shape, and surface properties of nanoscale particles were also discovered to be influenced by the cellular uptake pathways of NPs. With increased understanding of the elements and behaviors of NP toxicity in the environment and among life forms, nano toxicologists have recognized the necessity for enhanced information about the atomic intuitive of NP with organic frameworks [123]. They will be better able to anticipate the potentially hazardous properties of innovative nanomaterials as a result, ensuring the safe and effective advancement of nanotechnology. Given that NP poisonous quality has been demonstrated to depend on anions and cations, pH levels, and other naturally occurring components, natural nanotoxicology is extending the applicability of testing conditions (such as media composition, presentation concentrations, and term) to those important to the environment and life form physiology. The security evaluation of nanoparticles created for application in biotechnology, natural bioremediation, wastewater treatment, agribusiness, and nanomedicine is another important topic of nanotoxicology that has lately gained momentum. Nanotoxicology is essential for ensuring successful nano development across a range of applications and advancing the safe-by-design philosophy in nanotechnology [123]. Using a rebuilt standard water treatment framework with a semi-permanent supply of NPs, Aravantinou *et al.* [130] assessed the long-term harmful quality of zinc oxide nanoparticles to microalgae.

Like other metal oxide NPs, zinc oxide nanoparticles are well known for their ability to produce ROS and initiate apoptosis, and they have remarkable healing potential. Because of their characteristics, zinc oxide nanoparticles are serving as antimicrobial, antibacterial, and anticancer specialists. Zinc oxide nanoparticles were shown to offer synergistic advantages when used with various therapeutic regimens.

Clinical diagnostics and targeted medication delivery are being utilized more frequently because zinc oxide nanoparticles have several uses in the medical industry and for environment friendly purposes. Economically sound since they can be produced at cheap cost.

Conclusion

Biomedical nanomaterials have gained attention in the past decade due to their biological features and applications in various industries. Metal oxide nanoparticles, such as ZnO, have been used in antibacterial, drug/gene delivery, anticancer, cell imaging, and biosensing. Synthetic techniques have been used to meet demand,

but green synthesis, using plants, extracts, or microbes, offers environmental and financial advantages. This review summarizes recent developments in ZnO nanoparticle synthesis and biomedical uses.

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Graphical abstract

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التحضير الأخضر والتطبيقات الطبية الحيوية لجسيمات أكسيد الزنك النانوية

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في السنوات العشر الماضية، جذبت المواد النانوية الطبية الحيوية الكثير من الاهتمام. ونظرًا لخصائصها البيولوجية الواسعة والهامة واستخداماتها الطبية الحيوية، فقد سلطت الضوء على العديد من القضايا. هناك العديد من التطبيقات الطبية للجسيمات النانوية لأكسيد الفلز، بما في ذلك التطبيقات المضادة للبكتيريا، وتوصيل الأدوية/ الجينات، ومضادات السرطان، وتصوير الخلايا، والاستشعار الحيوي. في السنوات الأخيرة، استخدمت مجموعة متنوعة من الصناعات، بما في ذلك الصناعات الدوائية ومستحضرات التجميل والخرسانة ومضادات البكتيريا والنسيج، بالإضافة إلى صناعة السيارات، جزيئات أكسيد الزنك النانوية (ZnO NPs) كمواد رئيسية. ترتبط قدرة اكسيد الزنك النانوى ZnO NPs على إنشاء أنواع أكسجين تفاعلية وبدء برمجة الخلايا (موت الخلايا المبرمج) بالأنشطة المضادة للسرطان والبكتيريا. لذلك، من أجل تلبية الطلب المتزايد على اكسيد الزنك النانوى ZnO NPs، تم استخدام العديد من التقنيات الاصطناعية لإنتاجها. يتم الآن البحث عن بدائل إضافية ذات مزايا بيئية ومالية بسبب التكاليف الاقتصادية والبيئية المرتبطة بأغلبية طرق إنتاج اكسيد الزنك النانوى ZnO NP. ومن المثير للاهتمام أن التقنية البيولوجية للتوليف، والتي تستخدم النباتات أو المستخلصات النباتية أو الميكروبات كمصادر، قد أثبتت أنها مناسبة لتحضير اكسيد الزنك النانوى ZnO NPs بسبب مزاياها الطبية والصحية والبيئية والاقتصادية المتعددة. لخصت هذه الدراسة أحدث التطورات في التحضير والاستخدامات الطبية الحيوية لأكسيد الزنك النانوى NPs المصنوعة باستخدام التحضير الأخضر.

الكلمات الدالة: جسيمات أكسيد الزنك النانوية ، التحضير الأخضر، التطبيقات الطبية الحيوية، مضاد لمرض السكر ومضاد للميكروبات ومضاد للسرطان، أجهزة الاستشعار الحيوية.