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REVIEW ARTICLE

The Vast Biomedical Applications of Zinc Oxide Nanoparticles

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Abstract

Biomedical nanomaterials have gained a lot of attention in the last decade. They have emphasized various concerns due to their vast and significant biological properties and biomedical applications. Metal oxide nanoparticles offer a wide range of medicinal uses, including anticancer, drug/gene delivery, antibacterial, cell imaging, and biosensing, among others. Zinc oxide nanoparticles (ZnO-NPs) have been employed like a key material in a range of industries in last years, including medicine, cosmetics, concrete, antimicrobials, and textiles. the automotive industry, and cancer prevention. Anticancer and antibacterial effects are linked to the capability of ZnO-NPs to produce reactive oxygen species (ROS) and trigger cell programmed death (apoptosis). The following review articles summarize the different biomedical applications of ZnO nanoparticles.

Keywords: Nanoparticles; Zinc Oxide Nanoparticles; Antidiabetic; antibacterial.

Introduction

Nanoparticles and nanomaterials have a growing number of applications, and working with them has enabled a much deeper knowledge of biology [1, 2]. Zinc oxide nanoparticles (Zn-ONPs) are broadly utilized in a variety of sectors as much as their particular physical and chemical characters [3, 4]. Zn-ONPs also exhibit outstanding antibacterial, antimicrobial, and UV blocking capabilities. As a result, final fabrics containing Zn-ONPs in the textile industry display attractive UV and visible light resistance, antibacterial, and deodorant properties [5] .

Zinc is a naturally occurring element that plays an important role in the metabolism of man, animals, and plants [6]. Zinc is broadly recognized as an essential trace element that can be found in all body tissues, including bone, brain, muscles, and skin. Zinc is an essential component of many enzyme systems and plays an important role in protein and nucleic acid production, hematopoiesis, and neurogenesis [3, 4, 7, 8]. Nano-ZnO is more easily absorbed by the body due to small particle size of Zinc. As a result, nano-ZnO is widely used in the food industry. Zinc Oxide (ZnO) is also designated as a "GRAS" (Generally Recognized As Safe) approved by Food and Drug Administration (FDA) [9]. ZnO is broadly utilized in pharmaceutical, cosmetic, and medicinal applications and is acknowledged to be a valuable nutritional addition. Despite the fact that zinc oxide dust and fumes are typically considered safe, breathing them should be avoided. [6] ZnO is found as the mineral zincite in the earth's crust, but most of it is synthesized for commercial use. ZnO is made safe and compatible with human skin by adding it to fabrics and surfaces that come into touch with flesh. Zn-ONPs are broadly used in variance of industries, including UV light-emitting devices [10, 11], ethanol gas sensors [12, 13], photo-catalysts [14, 15], industries of pharmaceutical and cosmetics [16]. Non-toxic and self-cleaning are just a few of the benefits of ZnO-NPs [17], UV-blockers were used in sunscreens and a diversity of medical specialty practice because they are skin-friendly, antibacterial, and dermatologic associate degrees[18]. ZnO appears to have a high resistance to germs, and various studies have found that CaO, MgO, and ZnO have a significant antibacterial drug activity. [19] This is because of the creation of Reactive Oxygen Species (ROS) on the oxides' surfaces as summarized in Figure (1).

Various studies have utilized ZnO-NPs as a drug delivery mechanism in a variety of disorders. These nanoparticles have been shown to be capable of delivering drugs to a variety of cells and tissues [2]. ZnO-NPs have the probability to be employed as a bioimaging tool. Zn-ONPs have received a lot of attention in biomedical applications because of these features. Zn-ONPs, which have economic price and less toxic than other metal oxide NPs, have a broad range of medicinal practice, including anticancer, antimicrobial, and diabetic treatment; anti-inflammation; wound healing; and bioimaging [20-22]. Because of their great ultraviolet (UV)absorption and transparency for visible light, Zn-ONPs are efficient sunscreen agents [23, 24]. Other features, such as anticancer activity and antibacterial, have also been investigated as a result of their capacity to create (ROS) [25]. Zn-ONPs are effective drug carrier systems in addition to their intrinsic biological features. Bulk ZnO has also been certified as GRAS material by the US Food and Drug Administration (FDA) and Zn-ONPs bigger than 100 nm are regarded biocompatible, indicating that they could be used for drug administration. [26]. Another metal NPs, for example as iron oxide NPs, have anticancer activity as well, although no well-defined antibacterial or UV-absorbing properties have been found. In addition, when make a comparison to other metal oxide NPs, Zn-ONPs are more affordable, biocompatible, and low poisonous, which further enhance its application potential [27, 28]

Biomedical Applications of ZnO Nanoparticles

As a recent form of Lower cost, less-toxic nanomaterial, Zn-ONPs have generated a lot of interest in biomedical domains like antioxidant, anticancer, antibacterial, anti-inflammatory activities, and anti-diabetic, as well as bioimaging and drug administration [9, 21]. This study summarizes some developments in the use of Zn-ONPs in biomedical applications. Zn-ONPs with a diameter of less than 100 nm are deemed biocompatible, which supports their biomedical applications and is a strong motivator for biomedical research as summarized in Figure (2) and with special emphasis to their mechanism of action as summarized in Table (1).

1. Anticancer Activity

Chemotherapy, radiation, and surgery have all been used to treat cancer in the past few decades. Cancer is a disease marked by uncontrolled malignant cell proliferation. Although all of these drugs appear to be efficient for killing cancer cells in theory, they all have a long list of negative side effects [29]. Zn-ONPs cause malignant cells to die without causing cytotoxicity in healthy cells [30, 31]. Before Zn-ONPs may be used in medicine, a number of issues must be addressed, including a best understanding of the mechanism of their specific cytotoxic effect and the shortage appropriate biocompatible dispersion techniques [32]. ZnO-NPs have been found to have deleterious outcome on the vitality of primary human T cells at concentrations that are noxious to both gram positive and gram negative bacteria, according to a study mentioned by Reddy *et al.* [33]. According to many studies, these nanomaterials are innocuous to grown human dermal fibroblasts, but they are harmful to metastatic tumor cells [34] and vascular endothelial cells [35]. At the same time stimulating programmed cell death (apoptosis) in neural stem cells. Nanomaterial-based nanomedicine has nowadays showed the capacity to resolve these negative outcomes because of its high biocompatibility, cancer targeting, easily of surface functionalization, and drug distribution capacity. Adults require Zn^{2+}, and ZnO nanoparticles are regarded harmless in Living organism. Due to these benefits, Zn-ONPs can be used as biodegradable and biocompatible nanoplatforms, as well as being investigated for cancer therapy [36, 37]. Zn-ONPs show anticancer action via causing the production of ROS as well as promoting apoptosis. Furthermore, the electrostatic characteristics of Zn-ONPs, which have been used for anticancer activity, are a helpful feature. Because of the chemisorbed neutral hydroxyl groups on their surface, Zn-ONPs have unique surface charge behavior. In an aqueous solution with a high pH, protons (H+) flow away from the particle surface, generating a negative charge on surface with oxygen atoms that are only partially bonded (ZnO). At lower pH, protons from the surrounding environment are transported to the particle surface, resulting in a positive charge on surface (ZnOH2+) [9, 38]. Zn-ONPs have an isoelectric point of 9–10, under physiological parameters they have a high positive surface charge [39]. Cancer cells, on the other hand, have substantial negative membrane potentials and on the surface of their membranes they have a high concentration of anionic phospholipids (phosphatidylserine) [40, 41]. Cancer cells interact with positive charge Zn-ONPs because of electrostatic interactions that boost cellular absorption, phagocytosis, and cytotoxicity [9].

1.2. Anticancer by Autophagy

Autophagy is a catabolic process which is strictly controlled that is triggered by many stressors such as damaged organelles, ROS, protein aggregation and anticancer drugs. Highly cellular damage can cause cancer cell apoptosis by cellular self-consumption and extending autophagy, which results in cell death [42, 43]. As a result, autophagy enhances cell viability, also activates death pathways in cancer cells making it a key event in nanoparticle induced cytotoxicity.

1.3. Anticancer by using Zn-ONPs in drug delivery.

The use of nanoparticles in fouced drug deli very raises the potential for cancer treatment w hich are safer and more effective. By targeting specific areas on cancer cells, nanoparticle based drug delivery has the potential to lower the overall amount of medications used and, as a result, prevent undesirable side effects [9, 44]. Zn-ONPs are appealing owing to their lower toxicity and biodegradability when compared to other nanomaterials. The usage of Zn-ONPs in cancer medicine delivery has attracted a lot of interest. Drugs such as curcumin, doxorubicin, paclitaxel, and baicalin, as well as DNA fragments, may be loaded onto ZnO nanoparticles to demonstrate improved toxicity, solubility, and delivery into cancer cells compared to individual compounds [45-48]. Previous research has suggested that ROS and autophagy have a role in Zn-ONPs cytotoxicity. The regulative mechanisms that govern autophagy and ROS, on the other hand, have yet to be found. Zhang *et al.* [49] explored the control mechanism of autophagy and the relationship between autophagy and ROS in lung epithelial cells mediated with Zn-ONPs.

1.4. Targeting Functionalization

Apart from specificity and localization, targeted nanoparticles (NPs) offer additional therapeutic benefits such as large payload, multidrug conjugation, facile discharge kinetics adjusting, selectiveness localization, and bypassing multidrug resistance mechanisms [50]. Many functionalization approaches for nanoparticle modification have been documented in conductive to improve the targeting effects and selectivity against cancer cells. Surface modification of Zn-ONPs increased their persistence and specificity against certain cancer cells even more. Surface modification of Zn-ONPs with a variety of biological substances, such as folic acid, proteins, peptides, nucleic acids, hyaluronan, and so on, is the focus of the research [51-55]. The anticancer activity of Zn-ONPs was unaffected by the biocompatible coating, However, the ability to target cancer cells was enhanced, and the protection against normal cells has been improved.

2. Antibacterial Activity

Zn-ONPs can be employed as an antibacterial material due to its remarkable properties, which include a large specific surface area and the ability to kill a wide range of pathogens. However, the antibacterial action of Zn-ONPs has just lately been discovered. In the formation of nanoscale systems and microscale for therapeutic uses, Zn-ONPs have accepted to be a potent drug. Although Zn-ONPs appear to have greater medical curative activity than microparticles, the exact mechanisms of action of drug have yet to be determined [56]. The Zn-ONPs have germicidal properties against both gram negative and gram positive bacteria [57]. They also have antimicrobial efficacy in the face of spores that can withstand high temperatures and pressure. The pharmacological action of Zn-ONPs is dependent on their concentration and size; with crystalline structure and particle form have little effect. As a result, it is revealed, the greater the extent and concentration of nanoparticles, the greater the therapeutic pharmacological activity. The mechanism of Zn-ONPs' medical pharmacological action is still unknown in its totality. In their investigation, some researchers stated that the production of hydrogen peroxide is the primary issue with medical action, while others suggested that particle adherence on the microorganism surface owing to fixed forces could be other factor [32]. With increased particle dose, treatment period, and synthesis technology, nanoparticle efficacy will rise. Furthermore, the particulate size variability and surface area to volume ratio of green Zn-ONPs are undeniably the source of the significantly improved antibacterial activity revealed by this data. According to the researchers, unpracticed Zn-ONPs had the ability to be employed efficiently in food safety applications and agricultural, as well as to solve future medical challenges [58]. Gram negative bacteria such as *Escherichia coli (E. coli)* and Gram positive bacteria such as *Staphylococcus aureus (S. aureus)* are now the most commonly used model bacteria to investigate Zn-ONPs antibacterial activity [33, 59]. Some other Gram-negative bacteria such as *Vibrio cholerae (V. cholerae)* [60]. *Pseudomonas aeruginosa (P. aeruginosa)* [61, 62], *Proteus vulgaris (P. vulgaris)* [63], and other Gram positive bacteria such as *Enterococcus faecalis (E. faecalis)* [64], and *Bacillus subtilis (B. subtilis)* [65] are also investigated. Jiang *et al.* [66] recorded that Zn-ONPs have antibacterial properties against *E. coli*. Zn-ONPs with mean range size of 30 nm were discovered to destroy cells by directly touching the membrane's phospholipid bilayer and damaging membrane integrity, Zn-ONPs' ability to kill bacteria could be inhibited by the addition of radical scavengers like mannitol, vitamin E, and glutathione, possibly indicating that ROS generation was essential for Zn-ONPs' antibacterial effects. However, it did not appear that Zn^{2+} released from ZnONP suspensions had an antimicrobial impact. Reddy *et al.* [36] made Zn-ONPs with a diameter of 13 nm and tested their antibacterial activity against *E. coli* and *S. aureus* germs, according to the results, Zn-ONPs fully stopped the development of *S. aureus* at doses of less than 1 mM, but completely resisted the growth of *E. coli* at roughly 3.4 mM [33].

The Gram-negative bacterium *V. cholera* infects the intestine and causes cholera, a deadly diarrheal disease, primarily affects people in impoverished nations [60, 67]. Sarwar *et al.* [68] investigated the impact of Zn-ONPs on *Vibrio cholerae* (two cholera bacteria biotypes) (classical and El Tor) with the goal of developing nanomedicine against cholera. Zn-ONPs were found to be more effective in resisting the growth of the El Tor (N16961) biotype of *V. cholera*, which was linked to the formation of ROS. These outcomes would harm bacterial membranes, enhance permeabilization, and alter their shape significantly. In cholera toxin (CT) mouse models, Zn-ONPs exhibit antibacterial properties. Zn-ONPs have been found to have the ability to cause the CT secondary structure to gradually collapse and interact with CT through interfering with CT attachment to the GM1 gangliosides receptor [69]. The specific antibacterial mechanism of Zn-ONPs remains unknown. As a result, understanding it in depth provides a lot of theoretical and practical significance. We expect Zn-ONPs will be investigated as antibacterial agents in the future, such as lotions, creams, and mouthwashes. Also, it can be coated on a variety of substrates to inhibit germ from adhering to, propagating through, and reproducing in biomedical application. The capacity of Zn-ONPs to cause oxidative stress also contributes to their antibacterial activity. The thiol group of respiratory enzymes interacts with Zn+ ions produced by ZnO, limiting their function. Zn-ONPs have been shown to influence the cell membrane and lead to the generation of ROS. When bacteria contact with Zn-ONPs, they uptake Zn+, which suppresses respiratory enzymes, produces ROS, and free radicals, causing oxidative stress. ROS causes irreversible damage to bacterial membranes, DNA, and mitochondria, culminating in bacterial cell death [70]. Ghasemi and Jalal [71] reported that Zn-ONPs were evaluated for their effect on the efficacy of the traditional antibiotics ciprofloxacin and ceftazidime, also their mechanisms of action against resistance *Acinetobacter baumannii*, an opportunist bacterium that causes pneumonia and meningitis. The antibacterial activity of both medicines enhanced when presence of a sub-inhibitory concentration of Zn-ONPs, according to the findings. Combining antibiotics with Zn-ONPs boosted antibiotic absorption and converted bacterial cells from rods to cocci. The production of ROS and DNA alteration were also reported. These results suggest that Zn-ONPs and antibiotics can be used in combination to treat bacterial infections. It has also been found that Zn-ONPs improve the photosensitizer crystal violet's (CV) antibacterial activity [72].

Both Gram-negative and Gram-positive microbes exhibit antibacterial activity in response to Zn-ONPs [73]. Zhang *et al.* [74] investigated both dosage- and moment-dependent phenotypic bacterial reaction to Zn-ONPs using Surface enhanced Raman spectroscopy (SERS) method. Their findings revealed spectral change profiles that were both clear and informative. Significant changes were seen in smaller dose limit rather than bigger dose limit, demonstrating a decrease in Zn-ONPs bioavailability as dosages were increased. Within 0.5 hour, rapid activity was established, and smaller doses and lengthy exposure times had similar outcome to large doses.

3. Antimicrobial Potential of Zn-ONPs

In order to overcome multi-drug resistance, Zn-ONPs have been researched for the creation of next-generation nano-antibiotics against pathogenic microbes [75, 76]. These nanoparticles exhibit distinctive morphology, particle size, crystallinity, and porosity characteristics [77]. Based on these features, Zn-ONPs have a broad spectrum of antimicrobial activity against a variety of microbes, including the *M13 bacteriophage*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *and Pseudomonas aeruginosa* [78-81]. In both non-clinical and clinical settings, they can be used with antibiotics and inflammatory medications to increase antimicrobial effect against pathogenic microbes without antibiotic resistance [81, 82].

ZnO is being studied as a medication agent in formulations at the micro and Nano scale levels, although the specific mechanism of drug action is unknown, it has been claimed that the majority of reasons of cell ballooning are the rule of ROS generated on particle surfaces, zinc ion discharge, membrane malfunction, and nanoparticle acquisition area unit. Processing of Zn-ONPs at high temperatures has a significant impact on their medicinal action, whereas treatment at lower temperatures has a reduced impact [6] Zn-ONPs are being investigated in conjunction with medical procedure ablation protocols. Nanoparticles will give antineoplastic drug specialized that shows a synergistic antineoplastic action in the presence of heat, and they may even be photographed to obtain accuracy in medicinal assistance. Furthermore, lead to a stronger thermal impact on neoplasm ablation. Several studies have shown that understanding the molecular process underlying tumor-mediated nanoparticle ablation could aid in the development of nanoparticles with the right composition and characteristics to enhance the ablation property [83-85]. Mechanisms of antimicrobial actions of ZnO materials have been recorded in association with particular interactions based on their unique physicochemical properties of (a) Zn^{2+} ion release, (b) adsorption, (c) ROS generation [86, 87], and the intracellular responses in microorganisms of (d) energy metabolism inhibition; (e) lipid peroxidation, Nanomaterials 2021, 11, 263 8 of 35 and cell membrane damage; and (f) DNA replication disruption, and DNA break [88, 89]. Due to disruption of enzyme systems and interference with metabolic activities, the Zn^{2+} ions produced from ZnO-NPs/MPs cause an antimicrobial response in microorganisms [90, 91]. Additionally, ZnO-NPs/MPs have the ability to adsorb particles to the bio-membrane through a charge-charge interaction and generate ROS as photocatalysts when exposed to UV and visible light [77, 92-94]. Zn-ONPs/MPs with positively charged surfaces interact with microorganisms with negatively charged cell walls or bio-membranes [95] After adsorption, they are ingested by the bacteria, causing cell integrity to be lost as a result of membrane or cell wall rupture. They also mediate oxidative stress due to lipid peroxidation, which causes DNA damage. Depending on their physicochemical properties, such as shape, particle size, and porosity, Zn-ONPs/MPs have a variable susceptibility to pathogenic bacteria based on the basic modes of action [77, 95-97] Zn-ONPs, and occasionally MPs; have improved antimicrobial activity even toward dangerous viruses. They also offer wide-spectrum antimicrobial activity that can be tailored for several treatment options and used to increase their suitability as commercial and clinical translation platforms when combined with other antibiotic medicines, metal oxide NPs/MPs or metal doping, and other biomaterials [98].

4. Anti-diabetic activity

Zinc has a key role in insulin storage, biosynthesis, and secretion; hence Zn-ONPs have been studied for their anti-diabetic properties. Zn-ONPs were found to have good anti-diabetic efficacy than ZnSO4, as evidenced by enhanced insulin levels, glucose disposal, and zinc state when compared to ZnSO4 [99]. Wahba *et al.* [100] recorded that ZnO-NPs efficiently corrected diabetes stimulated pancreatic disease, as evidenced by ultrastructural and structural improvements and biochemical normalization of serum insulin and blood glucose. In another experiments, ZnO-NPs were combined with the anti-diabetic medicines red sandalwood and vildagliptin to boost their effectiveness [101, 102]. By breaking down oligosaccharides and disaccharides, α-amylase enzyme secreted in the pancreas and α-glucosidase enzyme secreted in the intestine produced monosaccharide (glucose) [103] Diabetes mellitus is a metabolic disorder caused by a defect in insulin secretion or activity. It is characterized by persistent hyperglycemia and ineffective carbohydrate metabolism [104]. As a result of insulin's poor performance, blood glucose levels in diabetes patients continue to be elevated. Therefore, it is essential to regulate blood glucose levels by blocking the enzymes α-glucosidase and α-amylase. There are numerous medications available today to suppress the α-amylase and α-glucosidase enzymes, but they also have some negative effects [105].

Ci-ZnO-NPs inhibit α-amylase and α-glucosidase enzymes, for α-amylase, the proportion of inhibition ranged from 20% (20 g/ml) to 74 percent (100 g/ml), while for α-glucosidase, it ranged from 36% (20 g/ml) to 82 percent (100 g/ml). Compared to α-amylase, α -glucosidase had a higher rate of inhibition [106].

5. Antifungal activity

ZnO-NPs are also excellent antifungal agents in addition to their antibacterial properties. Surendra *et al.* [107]. synthesized ZnO-NPs from M. oleifera, which were harmful to two plant disease strains, *Sclerrotium rolfii* and *Alternaria saloni*. Gunalan *et al.* [108] investigated the antifungal action of Zn-ONPs in a variety of fungal strains and recorded that they were toxic to plants and foodstuff pathogens in the following order: *Rhizopus stolonifera* > *Aspergillus flavus* > *Aspergillus nidulans* > *Trichoderma harzianum*. As a result, the scientists speculated that ZnO-NPs could be useful in the agricultural and food industries. ZnO-NPs have a concentration dependent influence on *Candida albicans* viability, according to Lipovsky *et al.* [109]. ZnO-NPs (0.1 mg/ml) decreased *C. albicans* vitality by >95 percent. Adding visible light to ZnO-NPs increased yeast cell death even more.

6. Anti-Inflammatory activity

The effectiveness of nano-ZnO and bulk-ZnO was investigated by Ilves *et al.* [110]. based on ZnO's anti-inflammatory properties and found that only nano-ZnO could permeate the deepest layers of allergic skin. Nano-ZnO also suppressed local skin irritation and promoted the synthesis of IgE antibodies in the system. According to the authors, this outcome is the consequence of nonspecific reactions triggered by liberated Zn^{2+} impairing B cells' ability to produce IgE.

7. Treatment of a range of different skin conditions

Zinc Oxide is commonly found in products that used in treatment of a variety of skin disorders such as diaper rash powder, barrier creams, hemimorphite cream, antimicrobial ointments, and anti-dandruff shampoos. It's also a component of tape (known as "zinc chemical compound tape"), which is utilized by sport manas a bandage to prevent soft tissue damage during exercises [111]. ZnO-NPs can be used in creams, ointments, and lotions to protect the skin against sunburn and other skin injuries induced by UV light. It's the most broad-range UVA and UVB reflector that the Bureau has certified for use as a sunscreen, and it's entirely photo-stable [112].

8. Drug delivery

Drug delivery has been proved as an effective instrument in the therapy of many diseases including cancer, among the various uses of nanotechnology [1, 2]. One of the most essential systems in medicine administrations is nanoparticles (NPs). In several researches, ZnO-NPs were employed for medication delivery in a variety of disorders [1, 2]. In a study, Yuan *et al.* [113] used ZnO quantum dots as a medicine administration device to target doxorubicin in HeLa cells. To improve the nanomaterial stability, they encased ZnO-NPs in chitosan. Their findings suggested that drug delivery technology could be utilized to efficiently deliver doxorubicin to cancer cells [113]. Another important feature of NPs' application is their usage as carriers for gene transport to various cells, specially malignant cells [2]. The usage of this technology for gene transfer comes with several benefits. For example, putting plasmid-containing genes on the surface of NPs could allow for safely and effectively gene delivery to the recipient tissues [1, 2].

9-Bio-imaging

Using this technique to distribute genes has several benefits. For example, plasmid encoded genes expressed on the surface of NPs may ensure that genes are transported safely and efficiently to the receiving tissues [1, 22]. Different forms of ZnO nanostructures have been identified in last years, including NPs, nanotubes, nanorods, and nanorings. Researchers are interested in using ZnO-NPs as bio-imaging agents [1, 22]. This feature has a variety of biological and medicinal uses and can be used at various levels. For example, luminous ZnO-NPs, also known as ZnOQDs, may have favorable photophysical properties [1, 22].

ZnO is generally considered to be a safe compound. ZnO has been used in sunscreen goods and as a food ingredient in food packaging. As a result, ZnO-NPs' luminous characteristics could be exploited in a variety of biological and medicinal applications. [1, 2, 22].

The nanotoxicological effect of ZNO-NPs

For instance, ZnO, which is typically thought of as a water insoluble compound, was demonstrated to exert toxicity through the release of Zn-ions in the case of ZnO nanoparticles, and it was found that the cellular uptake pathways of NPs were dependent on the size, shape, and surface characteristics of nanoscale particles. Nanotoxicologists have acknowledged the need for improved knowledge about the molecular interactions of NP with biological systems in order to better predict the potential toxicity of novel nanomaterials and ensure the safe and sustainable development of nanotechnology as knowledge on the mechanisms and behavior of NP toxicity in the environment and organisms has grown [114]. Given that NP toxicity has been shown to depend on interactions with organic matter in the environment, anions and cations, pH levels, and other environmental factors, environmental nanotoxicology is moving in the direction of increasing the relevance of testing conditions (e.g., media composition, exposure concentrations, and duration) to those relevant to the environment and organism physiology. The safety evaluation of nanomaterials created for use in biotechnology, environmental bioremediation, wastewater treatment, agriculture, and nanomedicine are another significant area of nanotoxicology that has gained traction in last years. In order to ensure effective nano innovation across a wide range of applications and to enable the safe-by-design approach in nanotechnology, nanotoxicology plays a significant role not only in the risk assessment of purposefully or inadvertently created nanomaterials [114] The long-term toxicity of ZnO-NPs to microalgae was evaluated by Aravantinou *et al.* [115] utilizing a simulated natural water treatment system with a semi-continuous supply of NPs.

Table 1. Biomedical application of ZnO-NPs.

Biomedical Applications of ZnO Nanoparticle	**Mechanism of action**	**Reference**
1-Anticancer Activity	In human liver cancer cell (HepG2) →↑ p53, Bax (mRNA and protein) and ↓ caspase-3, DNA Fragmentation, bcl-2.	[30, 31]
	↑ ROS →↑ cytoplasmic trigger of calcium ions and ↑ reaction with the cytoplasmic membrane → loss of membrane integrity →↑ calcium exit via membrane channels.	[30, 31]
2-Antibacterial Activity	The oxidation of fatty acids →↑ lipid peroxides chain reaction → disruption of plasma and organelle membranes → cell death.	[32]
3-Antimicrobial Potential of ZnO-NPs	Cell swelling due to →↑ROS, zinc oxide release and membrane dysfunction.	[6]
4- Antidiabetic activity	↑ phosphorylation of insulin receptor B-subunit, ↑ phosphatidyl inositol 3-kinase (PI3-K) and stimulate protein kinase B (PKB) → regulation glucose metabolism .	[99]
5- Antifungal activity	↑ surface → oxygen species →↑ disruption of the membrane Pathogen die .	[108]
6-Anti-Inflammatory activity	Reduced Zn^{2+} ion → in Blood, Lymph node and spleen →↑ Abs →↑ B-cell driven IgE antibody production.	[110]
8-Drug delivery	Drug administration has proved as an effective instrument in the therapy of many diseases including cancer, among the various uses of nanotechnology.	[1, 2]
9-Bio-imaging	This feature has a variety of biological and medicinal uses and can be used at various levels. For example, luminous Zn-ONPs, also known as ZnO-QDs, may have favorable photophysical properties.	[1, 22].

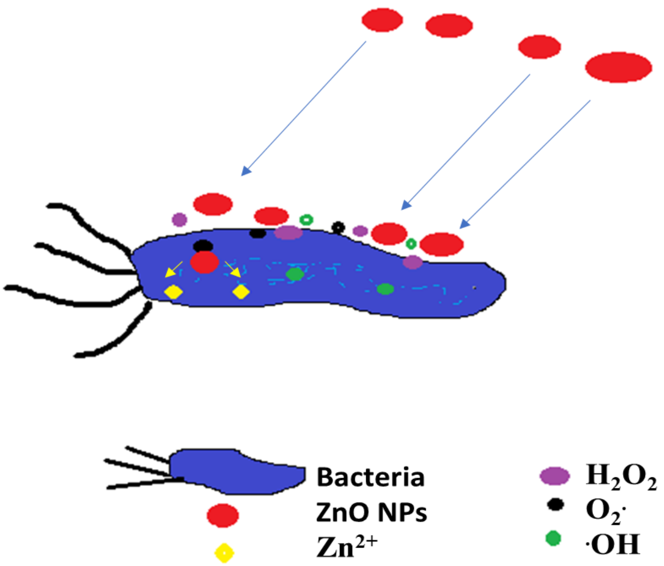

Figure 1: Schematic diagram of antibacterial activity of Zn-ONPs.

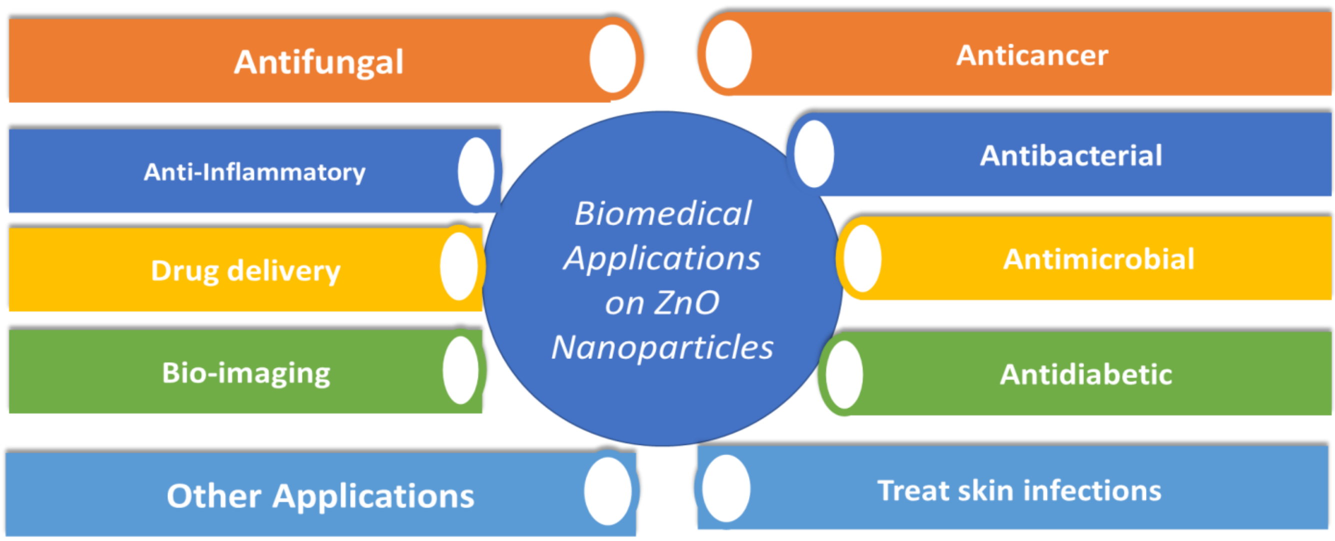

Figure 2: Biomedical application of ZnO Nanoparticles.

Conclusions

ZnO-NPs are known for their ability to create ROS and trigger apoptosis, like other metal oxide NPs, offer great medicinal potential. ZnO-NPs are useful as anticancer, antibacterial, and antifungal agents because of their properties. When loaded and given with other medicinal regimens, ZnO-NPs have been shown to have synergistic benefits.

Targeted drug delivery and clinical diagnostics are becoming more common as ZnO-NPs are a type of nanomaterial that has a lot of applications in medical purposes and green technologies, and they can be safely manufactured at a cheap cost.

Conflict of interest

All the authors have no conflict of interest to declare.

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الملخص العربي

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3- كلية الطب البيطري، جامعة بدر بالقاهرة، مدينة بدر، القاهرة، مصر.

4- قسم علم وظائف الأعضاء، كلية الطب البيطري، جامعة الزقازيق، 44511 الزقازيق، مصر.

اكتسبت المواد النانوية الطبية الحيوية الكثير من الاهتمام مؤخرًا. لقد أكدوا على مخاوف مختلفة بسبب خصائصهم البيولوجية الواسعة والهامة والتطبيقات الطبية الحيوية. تقدم الجسيمات النانوية لأكسيد المعادن مجموعة واسعة من الاستخدامات الطبية، بما في ذلك مضادات السرطان، وتوصيل الأدوية / الجينات، ومضادات الجراثيم، وتصوير الخلايا، والاستشعار الحيوي، من بين أمور أخرى. الزنك عنصر طبيعي يلعب دورًا مهمًا في عملية التمثيل الغذائي للإنسان والحيوان والنبات. يُعرف الزنك على نطاق واسع بأنه عنصر أساسي يمكن العثور عليه في جميع أنسجة الجسم، بما في ذلك العظام والدماغ والعضلات والجلد. يعد الزنك مكونًا أساسيًا للعديد من أنظمة الإنزيمات ويلعب دورًا مهمًا في إنتاج البروتين والحمض النووي، وتكوين الدم، وتكوين الخلايا العصبية. تم استخدام جزيئات أكسيد الزنك النانوية (ZnO-NPs) كمواد رئيسية في مجموعة من الصناعات في السنوات الأخيرة، بما في ذلك الأدوية ومستحضرات التجميل والخرسانة ومضادات الميكروبات والمنسوجات وصناعة السيارات والوقاية من السرطان. ترتبط التأثيرات المضادة للسرطان والبكتيريا بقدرة Zn-ONPs على توليد أنواع الأكسجين التفاعلية (ROS) وتحفيز الموت المبرمج للخلايا (موت الخلايا المبرمج). تلخص هذه المقالة المرجعية التطبيقات الطبية الحيوية المختلفة للجسيمات النانوية ZnO.