Review on the Medicinal Applications of Zinc Oxide Nanoparticles

P. Leema Rose, Department of Botany, Holy Cross College (Autonomous), Nagercoil, Tamilnadu.
Email: leemars148@gmail.com
S.Maneemegalai, Department of Biochemistry, Government Arts and Science College for Women(Affiliated to Bharathidasan University), Orathanadu, Tamilnadu.
Email: maneemegalai@gmail.com
M. Kulandhaivel, Department of Microbiology, Karpagam Academy of Higher Education, Pollachi Road, Coimbatore, Tamilnadu.
Email: kulandhaivel.m@kahedu.edu.in
P. Srinivasan, Department of Microbiology, Rathinam College of Arts and Science, Coimbatore, Tamilnadu.
Email: hod.microbiology@rathinam.in
J. Albino Wins, Department of Botany, Holy Cross College (Autonomous), Nagercoil, Tamilnadu.
Email: winsbt@gmail.com
Zoyeb Mohamed Zia, PG And Research Department of Zoology, The New College, Chennai. Tamilnadu.
Email: zoyebmdzia@gmail.com

Abstract

Nanotechnology has advanced dramatically over the last several decades. Zinc oxide (ZnO), which can have a wide range of nanostructures, has unique semiconducting, optical, and piezoelectric properties and has thus been studied for a wide range of applications. Low toxicity and biodegradability are important characteristics of ZnO nanomaterials. Zn2+ is an essential trace element for adults (a daily dose of 10 mg is recommended) and is involved in many aspects of metabolism. ZnO's surface is chemically rich in -OH groups, which can be easily functionalized by various surface decorating molecules. We summarised the current state of the use of ZnO nanomaterials for biomedical applications such as biomedical imaging (including fluorescence, magnetic resonance, positron emission tomography, and dual-modality imaging), drug delivery, gene delivery, and biosensing of a wide range of molecules of interest in this review article. Over the next decade, research in biomedical applications of ZnO nanomaterials will flourish, and much effort will be required to develop biocompatible/biodegradable ZnO nanoplatforms for potential clinical translation.
Keywords: Zinc oxide, nanomaterials, drug delivery, gene delivery.

Introduction

Nanomaterials are nanometer-sized falls with diameters ranging from 1 to 100 nm, and these materials have enhanced unique properties. Physical, chemical, and

biological methods are used to manipulate various types of nanoparticles. Nanoparticles are widely used as antimicrobial agents with antibacterial and antifungal properties against a variety of disease-causing pathogens [1]. Metal oxide nanoparticles have high antimicrobial activity compared to other types of nanoparticles due to their increased surface area to volume ratio. Zinc oxide nanoparticles are metal oxide nanoparticles that are an n-type semiconducting metal oxide. ZnO NPs are of great interest in research due to their wide range of applications in various fields of system, as well as their low cost of fabrication, safety, simplicity, and eco-friendliness [2]. ZnO nanoparticles exhibit catalytic activity, optic activity, anti-inflammatory activity, and wound healing activity due to the presence of a large band gap [3]. Furthermore, because of its UV filtering properties, ZnO NPs was commonly used in sunscreen lotions.

Zinc is widely recognised as one of the most important microelements required for vital functions. Zinc is absorbed primarily in the small intestine and then transported to blood plasma, where it is bound by albumins and globulins, or to the tissues, where it is deposited in zinc and cadmium accumulating protein. Zinc is found in the structure of metalloenzymes as well as hormonal complexes. Zinc's ability to participate in the processes of forming ligands with organic molecules explains why it is widely available in various biological systems. However, because zinc can be displaced by other cations accumulated in proteins, zinc distribution in tissues may change. Zinc transport and metabolism in the organism are distinguished by its rapid assimilation. Simultaneously, its deficiency is frequently caused by pathological conditions, and decreased zinc cation concentration may, in turn, influence vital processes in cells [4,5]. Zinc, for example, is important in biological processes such as cell growth and division, ceratogenesis, osteogenesis, immune response, wound repair (including postsurgical wounds), and pancreas reproduction and function.

ZnO Nanoparticles' Biomedical Applications

As a new type of low-cost and low-toxicity nanomaterial, ZnO NPs have piqued the interest of researchers in a variety of biomedical fields, including anticancer, antibacterial, anti-oxidant, anti-diabetic, and anti-inflammatory activities, as well as drug delivery and bioimaging applications. We summarised recent advances in the use of ZnO NPs in biomedicine here. ZnO NPs with diameters less than 100 nm are thought to be relatively biocompatible, which supports their biomedical applications and is a powerful property in promoting biomedical research.

Zinc Oxide Nanoparticles (ZnO NPs): A Potential Cancer Treatment

Because of their unique physical and chemical properties, zinc oxide nanoparticles (ZnO NPs) are one of the most exploited candidates in drug delivery, cancer diagnosis, and treatment. ZnO NPs are not only used to fight cancer, but they have also been shown to be very effective in fighting many other diseases and in a variety of other industries such as cosmetics, electronics, and the textile industry. ZnO nanoparticles can be created chemically, physically, or biologically. Precipitation, microemulsion, chemical reduction, sol-gel, and hydrothermal procedures are a few examples of chemical methods that require high pressure or temperature to be

maintained during the synthesis process. Physical processes, such as vapour deposition, plasma, and ultrasonic irradiation, are less common than chemical methods for producing ZnO NPs. Nonetheless, these procedures typically require a high level of energy and heavy equipment, raising the cost of the items. Biological synthesis is another method for producing ZnO NPs that has emerged as a more environmentally friendly technology. Regardless of the method used, all types of ZnO NPs have proven to be effective in cancer treatment, including diagnosis, treatment, and sustained/targeted release of anticancer drugs [6-8].

ZnO NPs are one of the most widely used metal oxide NPs in a wide range of industries and research institutions due to their numerous applications. The human body can easily absorb zinc due to the small particle size of nano-ZnO. Because ZnO NPs are less expensive and less toxic than other metal oxide NPs, they have a wide range of other medicinal applications, including antimicrobial, anti-diabetic, anti-inflammatory, anti-aging, wound healing, and bio-imaging. Because of their high biocompatibility, ZnO NPs can be used in a therapeutic setting for antibacterial, antifungal, antiviral, and anticancer properties. Several types of inorganic metal oxides, including TiO2, CuO, and ZnO, have been produced and are still being studied, but ZnO NPs are the most intriguing of these metal oxides because they are inexpensive to produce, safe, and simple to prepare.

Furthermore, any agent intended for human consumption for the treatment of various diseases must have the following characteristics. It must be nontoxic, not react with food or the container, have a pleasant flavour or be tasteless, and have no unpleasant odour. ZnO NPs are an example of an inorganic metal oxide that meets all of the criteria listed above, allowing them to be used safely as a medication, package preservative, and antibacterial agent. As a result, the US Food and Drug Administration (FDA) has classified ZnO NPs as "GRAS" (generally recognised as safe). ZnO NPs have a wide range of semiconducting capabilities due to their large band gap (3.37 eV) and high exciton binding energy (60 meV), including strong catalytic activity, optics, UV filtering, anti-inflammatory, and wound healing. Because of their UV filtering properties, they have also been widely used in cosmetics such as sunscreen lotions. ZnO NPs were first used in the rubber industry to improve the toughness and intensity of high polymers, as well as to provide anti-aging properties.

Because of their luminescence, ZnO NPs have gained interest in biomedical imaging. They have also piqued the interest of researchers in the development of diagnostic tools, as they can also be used in biosensing applications [9]. Figure 1 depicts the distinct properties of ZnO NPs that allow them to act as potent anticancer agents.

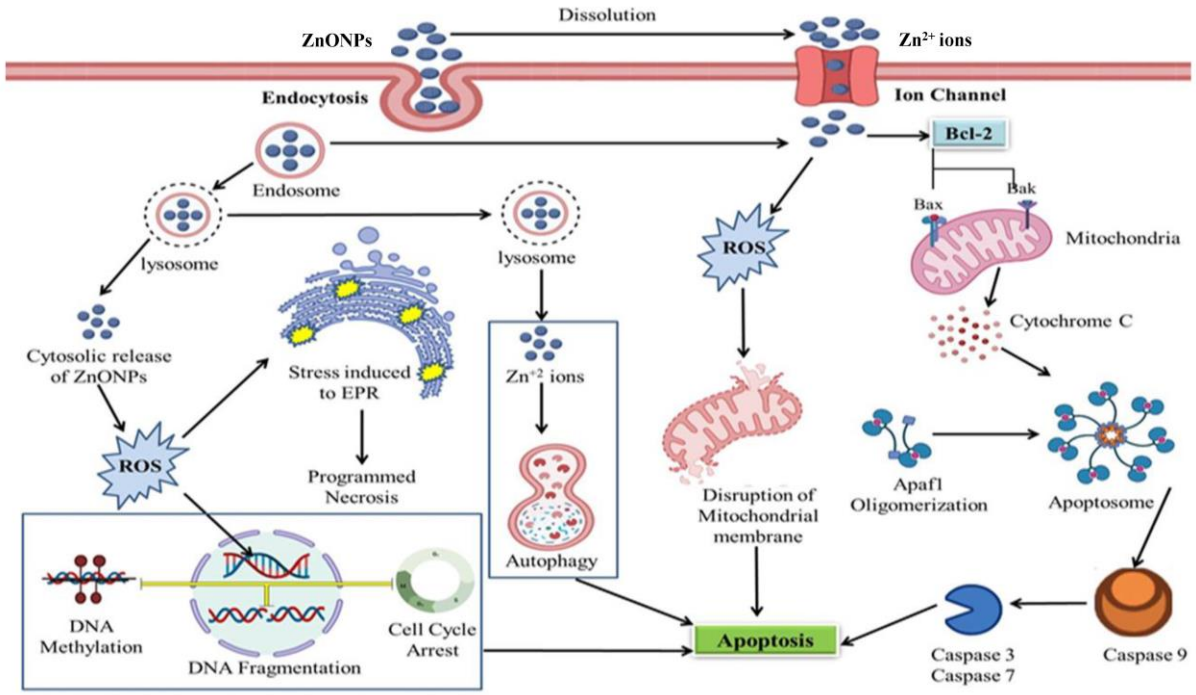

Figure 1.

Zinc Oxide Nanoparticles (ZnO NPs): Potential Candidate for Fighting Cancer

ZnO NPs for Diabetes Treatment

Diabetes mellitus is a serious public health issue, with the WHO estimating that more than 400 million adults worldwide had diabetes in 2014. Diabetes mellitus is a metabolic disease caused by the body's inability to produce insulin or the inefficient use of the insulin that is produced [10,11]. Zinc is a trace element that is abundant in all human tissues and tissue fluids. Zinc is well known for maintaining the structural integrity of insulin and for playing an active role in insulin secretion from pancreatic cells. It also aids in the synthesis, storage, and secretion of insulin [12]. As a result, ZnO NPs have been developed and tested for their anti-diabetic potential as a novel agent for zinc delivery.

Kitture et al. used a natural extract of red sandalwood (RSW) in conjugation with ZnO NPs as an effective anti-diabetic agent. The anti-diabetic activity of murine pancreatic and small intestinal extracts was evaluated using amylase and glucosidase inhibition assay [13]. The results showed that the ZnO-RSW conjugate had a slightly higher percentage of inhibition (20%) against porcine pancreatic amylase and was more effective against crude murine pancreatic glucosidase than either of the two elements (RSW and ZnO NPs). The conjugated ZnO-RSW inhibited glucosidase at 61.93 percent, while the bare ZnO NPs and RSW inhibited it at 21.48 percent and 5.90 percent, respectively. In 2015, Nazarizadeh and Asri-Rezaie conducted a study in diabetic rats to compare the antidiabetic activity and oxidative stress of ZnO NPs and ZnSO4. It was discovered that ZnO NPs with small dimensions had a much greater antidiabetic effect at higher doses (3 and 10 mg/kg) than ZnSO4 (30 mg/kg). It was demonstrated by a significant reduction in blood glucose levels, an increase in insulin levels, and an improvement in serum zinc status in a time- and dose-dependent manner. However,

severely induced oxidative stress was also observed by altered erythrocyte antioxidant enzyme activities, an increase in malondialdehyde (MDA) production, and a significant reduction in serum total antioxidant capacity, particularly at higher doses.

Hyperglycemia can directly exacerbate an inflammatory state by regulating C-reactive protein (CRP) and cytokines such as interleukins, both of which are involved in the development of cardiovascular diseases. To alleviate diabetic complications, Hussein et al. created ZnO NPs with hydroxyl ethyl cellulose as a stabilising agent [14]. It was discovered that ZnO NPs could significantly reduce MDA, fast blood sugar, and asymmetric dimethylarginine (ADMA) levels. In diabetic rats, the inflammatory markers interleukin-1 (IL-1) and CRP were significantly reduced after ZnO NPs treatment, concomitant with an increase in nitric oxide (NO) and serum antioxidant enzyme (PON-1) (Figure 2).

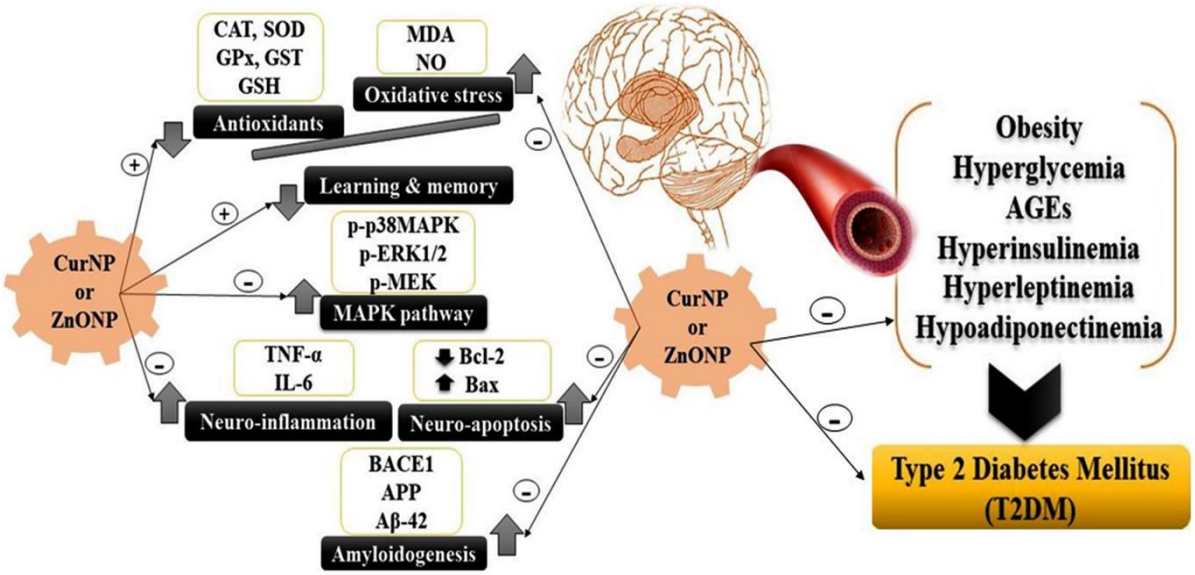

Figure 2: ZnO NPs for Diabetes Treatment.

Anti-Inflammatory Activity of ZnO NPs.

Inflammation is a component of the body's complex biological response to harmful stimuli such as pathogens, damaged cells, or irritants [15]. Because of the biological activities of zinc ions, the anti-inflammatory effects of ZnO NPs have received a lot of attention since the advent of nanoparticles.

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterised by impairment of skin-barrier functions [16,17]. It is caused by a complex interaction of genetic and environmental factors. Textiles have the most prolonged and intense contact with human skin. Wiegand investigated the role of ZnO-functionalized textile fibres in the in vitro and in vivo control of oxidative stress in Alzheimer's disease [18]. The study discovered that wearing the ZnO textiles overnight for three consecutive days improved AD pruritus and subjective sleep quality. This could be due to the ZnO textile's high antioxidative and antibacterial capacity.

In the mouse AD model, Ilves et al. investigated whether different-sized ZnO NPs could penetrate injured and allergic skin [19]. Their experiments clearly demonstrated

that only nanosized ZnO (nZnO) could reach the deep layers of allergic skin, whereas bulk-sized ZnO (bZnO) remained in the upper layers of both damaged and allergic skin. In the mouse model of Alzheimer's disease, nZnO exerted greater anti-inflammatory properties than bZnO by significantly lowering proinflammatory cytokines (IL-10, IL-13, IFN-c, and Th2 cytokines). These findings demonstrated that small-sized ZnO NPs had a significant impact on reducing skin inflammation in AD models.

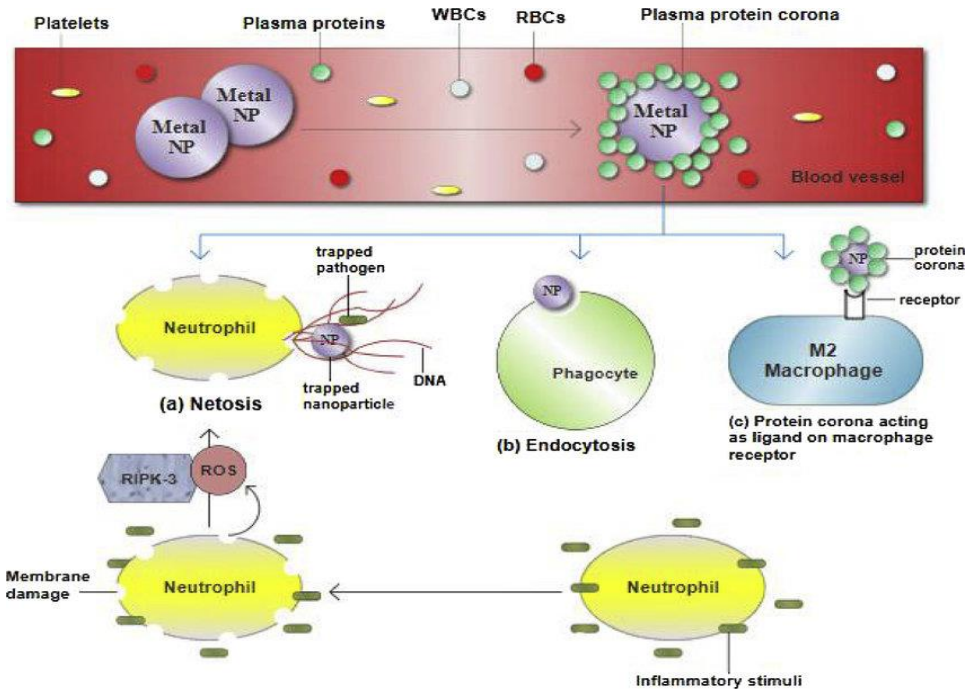

Figure 3: Anti-Inflammatory Activity of ZnO NPs.

ZnO NPs for Bioimaging

ZnO NPs have efficient blue emissions and near-UV emissions with green or yellow luminescence related to oxygen vacancies, extending their application into the bioimaging field [20]. Xiong et al. created stable aqueous ZnO polymer core-shell nanoparticles for the first time using a simple sol-gel method. In aqueous solutions, the ZnO polymer core-shell nanoparticles demonstrated high quantum yield and very stable broad photoluminescence. As shown in Figure 3, ZnO-1 (derived from LiOH) with an average size of 3 nm fluoresced green in human hepatoma cells, while ZnO-2 (derived from NaOH) with an average size of 4 nm fluoresced yellow. It's worth noting that at concentrations less than 0.2 mg/mL, these nanoparticles had no discernible toxicity for human hepatoma cells. Furthermore, the luminescence was very stable during cell culture, and the cells were still alive after 45 minutes. As a result, ZnO polymer core-shell nanoparticles can be used as fluorescent probes for cell imaging in vitro as a type of safe and inexpensive luminescent label [21].

Jiang et al. developed ZnO nanosheets for imaging cultured cells. They used ZnO nanosheets to treat drug-sensitive leukaemia line K562 cells, and the yellow-orange light emission was clearly visible around or inside the cells under UV irradiation (365 nm) at room temperature [22]. ZnO nanostructures were successfully attached to or

penetrated into the cells, implying that ZnO nanosheets emitting visible yellow-orange light could serve as a viable label for bioimaging.

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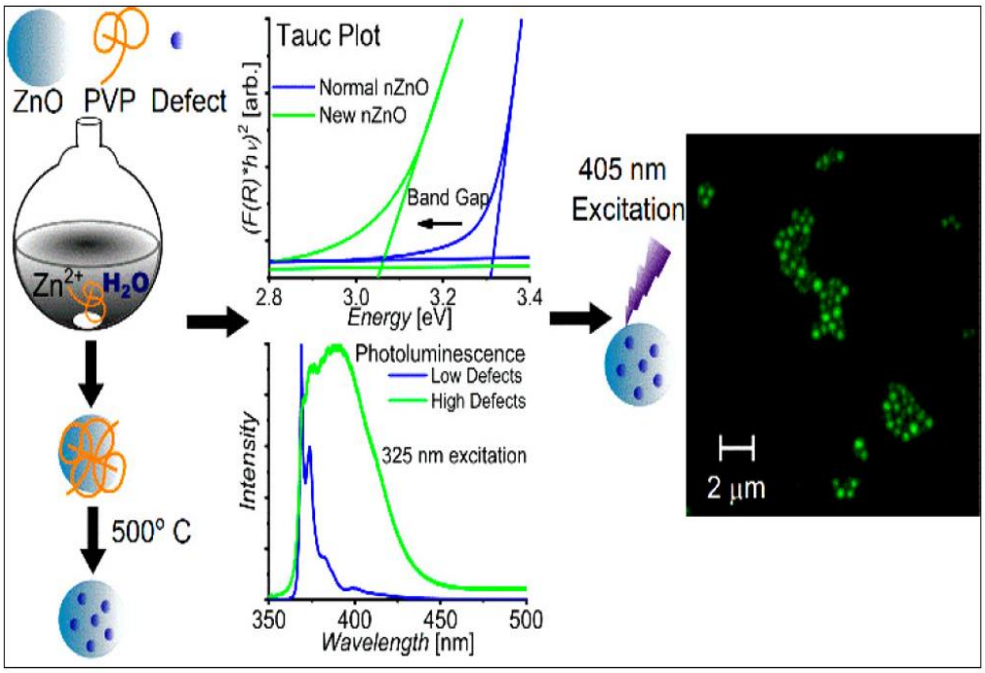

Figure4: ZnO NPs for Bioimaging.

Conclusion

Nanotechnology has had a transformative impact on biomedicine and has seen tremendous progress over the last several decades. Nanomaterials with sizes less than a few hundred nm, several orders of magnitude smaller than human cells, can exhibit properties distinct from molecules and bulk solids and provide unprecedented interactions with biomolecules on the surface and inside cells [131, 132]. ZnO nanomaterials are excellent candidates as biocompatible, biodegradable, "deliver and dissolve" nanoplatforms for cancer targeted imaging and therapy due to their many appealing physicochemical properties and tremendous potential for various biomedical applications. Despite the fact that this field of study is still in its early stages, various ZnO nanomaterials have already been evaluated for optical imaging and MRI in cells, as well as dual-modality MRI/optical imaging. The future of nanomedicine for in vivo imaging and therapy applications lies in multifunctional nanoplatforms combining both therapeutic components and multimodality imaging, so that therapeutic efficacy can be not only improved but also accurately monitored non-invasively over time. To date, no in vivo targeted imaging with ZnO nanomaterials has been reported, indicating that more research is needed in the near future.

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