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Review Article

Unveiling the Biomedical Applications of Zinc Oxide (ZnO) Nanoparticles: A Review Fostering on the Synthesis, Therapeutics and Imaging with Recent Developments

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Abstract

Zinc oxide nanoparticles (ZnO-NPs) in their many formulations have prompted an immense interest in nanomedicine and drug development. Numerous ZnO-NPs bioactive formulations demonstrate remarkable broad applications in deciphering their therapeutic effects and bioimaging. Their unique size, morphology-dependent properties and modifiable surface chemistry have made them promising candidates for translation into novel, alternative nanomedicines. ZnO-NPs demonstrate biocompatibility and are non-toxic with relatively required in-expensive production techniques. This review presents an in-depth comprehension of the synthesis, chemical and biological peculiarities of ZnO-NPs, including their varied manufacturing methods and their impactful applications in biomedicine. The physical, chemical and biological synthesis approaches that are unique for ZnO-NPs synthesis were comprehensively reviewed, followed by their applications in therapeutics (anticancer, antibacterial, drug delivery, skin treatment, antidiabetic and antioxidant), diagnostics (bioimaging and biosensor) and theranostics as well as their health hazards. ZnO-NPs exhibit antibacterial and anticancer activities, primarily through the liberation of zinc ions and generation of reactive oxygen species (ROS), which disrupt the cell membrane. Their anticancer properties are additionally apprised with an escalation in caspase 3/7 along with the modulation of pro- and anti-apoptotic proteins. ZnO-NPs are reviewed to attenuate hepatocellular carcinoma. Further, this article comprehended various *in-vitro* and *in-vivo* therapeutic effects of novel drug formulations of ZnO-NPs. It also delved into two fascinating areas: ZnO-NPs' performance in comparison with other NPs and the potential of ZnO-NPs heterostructures with 2D nanomaterials. The goal of this review is to inspire further research efforts to meet the growing needs of next-generation nanomedicine.

Introduction

Nanoscience and nanotechnology are active, rapidly expanding fields of research. Over the second half of the last century, the study and application of nanoscale structures and molecules have evolved from a mere vision to a reality.[1] These fields have progressed from recognitions and acknowledgments to implementations in various areas including medicine, food science, agriculture and the environment.[2-7] The fast development of nanomaterials is due to their minute size between 1–100 nm. This size is comparable to a virus and significantly smaller than human cells. Owing to the reduced particle size, nanomaterials exhibit attractive and unique physical, chemical and biological properties that are significantly different and absent from their bulk form. Nanomaterials being studied include zinc oxide nanoparticles (ZnO-NPs), which are among the most promising metal oxide nanoparticles.

Over the years, ZnO-NPs have gained significant popularity among industries and researchers due to their peculiar properties and versatility. They have been applied in various fields, notably rubber, cosmetics, pharmaceutical, optoelectronic, and environmental. Approximately 50% of the globally manufactured ZnO is used as an activator along with stearic acid during the tire vulcanization process annually.[8] Due to the high demand, ZnO-NPs have been explored to enhance the efficiency of the vulcanization

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process, concurrently improve the mechanical behavior of natural rubber and reduce the hazardous effects of excess zinc leaching to the aquatic environment.[9,10] Meanwhile, in the cosmetic field, ZnO is appreciated for its strong UV absorption properties at UVA and UVB wavelengths. Both bulk and nano-form ZnO have been approved for use in sunscreen formulations.[11] ZnO-NPs are also well-known raw materials in pharmaceutical applications, particularly in calamine lotion and baby rash products. In the optoelectronic industry, ZnO-NPs have gained much importance in applications such as light-emitting diodes, photovoltaics and photodetectors due to their good electrical conductivity, thermal stability and excellent optical transmittance in ultraviolet-visible-near infrared (UV-VIS-NIR) spectrum.[12] The wide range of applications of ZnO-NPs extends to environmental remediation, where they are used to address pollution and other environmental issues.[13,14] Based on the extensive applications of ZnO-NPs, the global market demand for ZnO-NPs is expected to grow and increase by USD 1.3 million in 6 years (USD 4.4 billion to USD 5.7 billion, 2019 – 2024).[15]

At present, ZnO-NPs are gaining fast, momentum in the nanomedicine field. They are considered promising candidates for the prevention, diagnosis, treatment and monitoring of medical conditions. The European Union (EU) has recognized the involvement of nanotechnology in developing novel medications to address unmet medical needs as Key Enabling Technology (KET). Global researchers are intrigued by ZnO-NPs due to their dynamic behavior, low toxicity and excellent biocompatibility. ZnO-NPs have demonstrated beneficial properties in areas such as antimicrobial, anticancer, antiviral, antioxidant, anti-inflammatory and anti-diabetic. Additionally, they are being explored for their potential in biological imaging, as nanocarriers for drug delivery, theranostics and coating of medical implants.[16,17]

In this review, we discuss the various synthesis approaches available, the recent advancements made by ZnO-NPs in the biomedical field and their associated toxicity concerns. This article aims to provide a fresh perspective on the multifaceted roles of ZnO-NPs, not only in known therapeutic and diagnostic domains but also in the emerging field of theranostics. Additionally, we endeavor to comprehensively compare ZnO-NPs with other NPs and delve into a futuristic approach: the development of heterostructures comprising ZnO-NPs and 2D nanomaterials. These two areas have received minimal attention in prior works similar to theranostics. We anticipate that this information will catalyze the efforts to expedite the translation of ZnO-NPs into impactful biomedical applications.

Physical, chemical and biological properties of ZnO-NPs

ZnO is naturally found within the earth's crust as mineral zincite. However, due to its rarity, most commercial products are produced synthetically. ZnO-NPs appear as a white, odorless crystalline powder with a molar mass of 81.38 g/mol. It exists exclusively in wurtzite type structure due to its sp3 hybridization-directed tetrahedral geometry and high bond polarity. ZnO-NPs are type II-VI semiconductors with unique inherent semiconductor properties, wide bandwidth of ~3.37eV and high excitation binding energy of 60meV at room temperature.[18] ZnO-NPs also possess low risk of bioincompatibility due to the presence of zinc. Zinc, the soluble form of ZnO, is an essential microelement for healthy defensive systems, cell growth and DNA creation. Meanwhile, the bulk ZnO has been affirmed as safe (GRAS) by the US Food and Drug Administration (FDA).

Synthesis of ZnO-NPs

ZnO-NPs can be synthesized via physical, chemical and biological approaches. The choice of the synthesis approach is driven by factors such as purity requirements, health and safety considerations, environmental implications and feasibility of scaling. Here, we explore the techniques within each approach for preparing ZnO-NPs.

Physical synthesis

Mechanical milling and laser ablation are widely used physical methods in synthesizing ZnO-NPs. Mechanical milling is a physical comminution technique where coarse-grained materials are reduced to nanosized particles by the repeated impact and friction of balls within a rotating milling chamber. Precise control over desired nanosized structures can be achieved by optimizing the type of mills, type and size of ball mill, the material of milling tools, milling media, milling duration and rotation speed as well as milling temperature.[19] Massoudi *et al.*[20] reported the fabrication of ZnO-NPs via high-speed ball milling with planetary magnetic ball mills. The team achieved a particle size of approximately 16% (148 ± 68nm) of the original size (929 ± 163nm) after 2h of milling at 1000rpm. As verified through X-ray diffraction patterns, no phase transformation was observed due to milling. Moreover, the synthesized ZnO-NPs exhibited antimicrobial activities against various human pathogens. Similarly, Mozharasi *et al.*[21] attempted to prepare ZnO-NPs with the same technique and demonstrated the safety of ZnO-NPs for consumption in broiler chicks up to 100 mg/kg. Conversely, laser ablation represents a form of physical vapor deposition technique. In Khashan *et al.*[22] work, zinc target was immersed in water and irradiated with a highly intense pulsed Neodymium-doped Yttrium Aluminium Garnet (Nd: YAG) laser system to produce the ZnO-NPs. From the study, the number of pulses influenced the morphologies and yield of ZnO-NPs. At the number of pulses of 25, 50, 75, 100 and 125, nanoplates, hexagonal-rod, spherical, agglomerates of spherical and flakes as well as nanowires were observed respectively. The prepared ZnO-NPs were also found to exhibit antibacterial, antiparasitic and anticancer properties. Chen *et al.*[23], on the other hand, demonstrated an alternative approach. Instead

of irradiating the zinc target immersed in media, the team subjected zinc powders suspended in water with magnetic stirring to pulse laser ablation for 1h and successfully obtained ZnO-NPs.

Chemical synthesis

Chemical synthesis entails the reduction of zinc precursor molecules to produce ZnO-NPs in solution or gas phases. Typically, chemical reagents are utilized to control the nucleation and growth of ZnO-NPs. Examples of chemical approaches include sol-gel, hydrothermal, solvothermal and chemical precipitation techniques. The sol-gel technique refers to the transformation of a sol (colloidal suspension) into gel over a succession of hydrolysis, poly-condensation, aging, drying and crystallization. This technique has been reported to be used in preparing ZnO-NPs[24] and polysaccharide-modified ZnO-NPs with wound-healing properties[25]. On the other hand, hydrothermal and solvothermal synthesis are two related techniques in synthesizing nanoparticles involving high vapor pressure and high-temperature conditions. Both procedures are carried out in closed reaction vessels. There is a difference between the two synthesis methods, in that hydrothermal synthesis uses water[26,27] and solvothermal synthesis uses organic solvents[28] when synthesizing ZnO-NPs.

The other technique, chemical precipitation, as its name suggests, involves the reaction between the precursor and alkaline reagent under controlled conditions, followed by centrifugation and filtration to collect the nanoparticles. In the study by Bekele *et al.*[29], different zinc precursors; zinc acetate dihydrate [$Zn(CH_3COO)_2{\cdot}2H_2O$], zinc nitrate hexahydrate [$Zn(NO_3)_2.6H_2O$] and zinc sulfate heptahydrate ($ZnSO_4.7H_2O$) were reduced by alkalizing agents, NaOH, KOH and polyvinyl alcohol (PVA) respectively. For each combination, the mixture was stirred for 2h at 60°C, cured in the oven for 10h at 160°C and calcinated for 6h at 300°C. From the analysis, semi-spherical to spherical particles of 31 to 40nm were observed. Similarly, Akpomie *et al.*[30] prepared irregularly shaped ZnO-NPs with an aggregated porous structure of 65.3nm in size with this technique.

Biological synthesis

Biological synthesis or green synthesis is a novel approach to nanotechnology, utilizing biological substrates such as plants and microorganisms as capping and/or reducing agents. This method offers biocompatibility, cost-effectiveness, eco-friendliness, sustainability, wastage reduction, maximum resource efficiency and the absence of hazardous chemical reagents. The key practices of green synthesis include using renewable and even more so, recycling and reusing resources. Plants are appealing in the green synthesis of ZnO-NPs due to their ease of access and abundance of phytochemicals. They are also deemed to be a safer option for biomedical applications due to their vast and long history of usage in ethnomedicine for healing purposes, such as antioxidants, anticancer, or antibacterial. A multitude of syntheses have been performed using extracts from different parts of the plants such as roots, leaves and flowers. These studies revealed the biodiversity of phytochemicals that potentially reduce zinc precursors to ZnONPs such as flavonoids, saponins, phenolics, polyphenols, alkaloids and anthocyanins.[31] Many studies have also explored the use of microorganism models like algae, bacteria, fungi and yeast in mediating the synthesis of ZnO-NPs. These microorganisms are attractive due to their ability to function as nano-factories either through intracellular or extracellular pathways.[32,33] Similar to plant-mediated synthesis, microbial-mediated synthesis requires the optimization of reaction factors such as temperature, pH, precursor concentration and time.[34] Microbial-mediated synthesis is associated with drawbacks pertaining to the screening, selection and isolation of microbes suitable for synthesis, complex downstream processing with intracellular synthesis and risk of contamination with improper purification. Despite the drawbacks, they could offer benefits in terms of reproducibility, cost, cleanliness and environmental friendliness.

Applications of ZnO-NPs in the Biomedical Field

Therapeutic functionality

Antibacterial agent

Antibiotic resistance is a global healthcare threat and the emergence of ZnO-NPs offers hope in eradicating the alarming multi-drug resistance (MDR) phenomenon. ZnO-NPs have gained significant recognition for their remarkable activity against a broad spectrum of bacteria. They are found to be effective against both Gram-positive (*Staphylococcus aureus, Staphylococcus epidermidis* and *Bacillus subtilis*) and Gram-negative (*Escherichia coli, Klebsiella pneumonia, Proteus mirabilis* and *Pseudomonas aeruginosa*) bacteria.[35-37]

Multiple distinctive mechanisms have been reported to be responsible for the antibacterial activity of ZnO-NPs as illustrated in Figure 1. They include (1) physical and/or electrostatic interaction between ZnO-NPs and bacteria surface leading to disruption of the cell membrane; (2) internalization of ZnO-NPs; (3) generation of ROS leading to oxidative stress, cell membrane disruption, subsequently DNA damage and cell death; and (4) liberation of zinc ions which diffuse across the cell membrane, interrupting with the normal functioning of bacteria cell and eventually results in cell death.[38-40] However, at present, there is no consensus on the exact mechanism of action of ZnO-NPs. The antibacterial properties of ZnO-NPs could be due to either one of the mechanisms or the involvement of interplay between all the above mechanisms. If the latter holds, ZnO-NPs potentially address the MDR issue as multiple gene mutations would be required to develop resistance to these NPs.

While debates on the plausible antibacterial mechanism remain, the antibacterial properties of ZnO-NPs have been proven to be modulated by their shape, surface area, size and concentration. In Talebian *et al.*'s[41] study, nanostructured

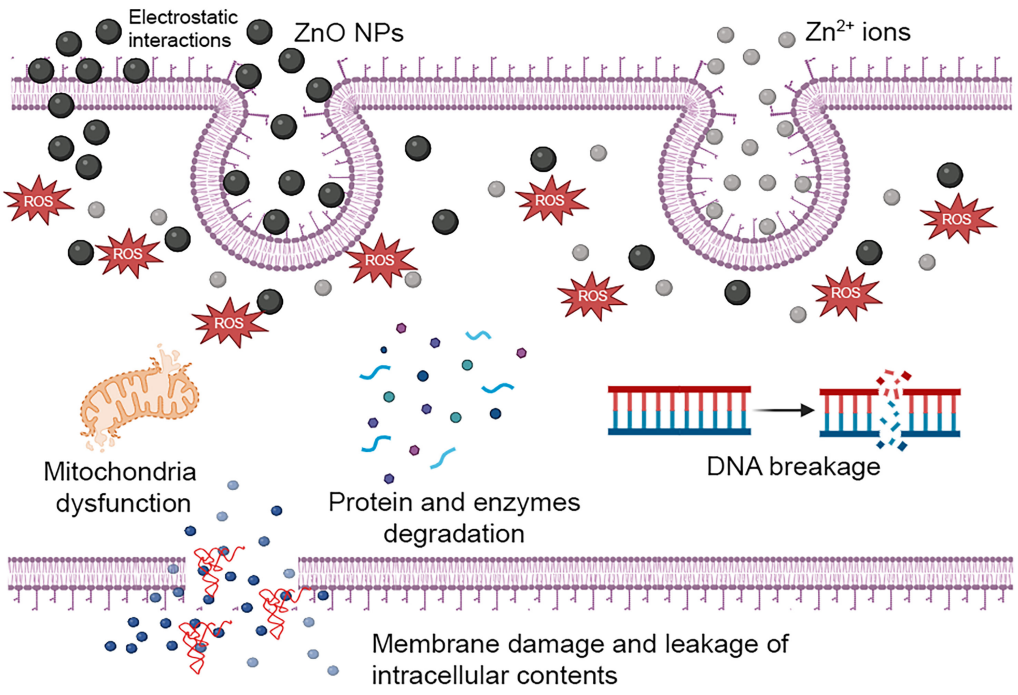

Figure 1. Plausible antibacterial mechanisms of ZnO-NPs.

flower-shaped ZnO exhibited superior antibacterial activity compared to spherical and rod-shaped ZnO against *S.aureus* and *E.coli*. The trend was attributed to the decreasing surface area; flower (28.8 m^2/g) > spherical (19.2 m^2/g) > rod (15.5 m^2/g). Similarly, Babayevska *et al.*[42] demonstrated the impact of surface area on the antibacterial properties of ZnO-NPs. The team noted that spherical (83.5 m^2/g) and rod (83.8 m^2/g) ZnO nanostructures were instead more effective than hierarchical flower-shaped (4.50 m^2/g) and tetrapod-shaped (29.4 m^2/g) ZnO on both bacteria. Furthermore, sheet-shaped ZnO with a higher surface area (18.5 m^2/g) presented more potent antibacterial activity than spherical (13.4 m^2/g) and flower-shaped (5.3 m^2/g) ZnO.[43] In terms of particle size and concentration, the antibacterial properties of ZnO-NPs are directly correlated with their concentration. Likewise, their activities are size-dependent. Abbasi *et al.*[44] demonstrated dose-dependent growth inhibition on *S.aureus, B.subtilis, E.coli, P.aeruginosa* and *K. pneumoniae* at 31.25 to 1000 µg/mL. Similarly, in Alvarez-Chimal *et al.*'s[45] study, the inhibition diameters of all eight bacteria strains tested (*S.aureus, S.epidermidis, E.coli, P.aeruginosa, Streptococcus mutans, Streptococcus sanguinis, Porphyromonas gingivalis* and *Prevotella intermedia*) were higher at ZnO-NPs concentration of 81400 µg/mL as compared to 40700µg/mL. In the same study, the impact of the size of ZnO-NPs (4 to 200 nm) was also evaluated. It was concluded that the bactericidal response was inversely correlated with the particle size. Smaller particle sizes are associated with increased specific surface areas, which facilitate penetration into the bacterial membrane and subsequently enhance antibacterial efficiency.

Due to the attractive antibacterial properties of ZnO-NPs, they have been incorporated into different PVA-based nanocomposites, including PVA/lipopeptides films[46], PVA/reduced graphene oxide/silk fibroin[47] and PVA/sodium alginate hydrogel.[48] These resulting nanocomposites demonstrated effective antibacterial properties and low toxicity, which could be utilized for wound dressing applications. Additionally, ZnO-NPs have been valued in dental applications as such, they are included in boron nitride nanosheets to obtain antibacterial dental resin composite that inhibits the growth of the dental pathogen, *S.mutans*.[49] ZnO-NPs have also been incorporated into hydroxyapatite coatings applied to stainless steel 316L bone implants to enhance the antibacterial properties and adhesion of the coating to the implant surface.[50] With the positive demonstration of antibacterial potential by ZnO-NPs, ZnO-NPs could potentially be the next nanomedicine to address bacterial infections and the current alarming concerns about antibiotic resistance. Further studies are still recommended for a clearer picture of their mechanisms against different types of bacteria and their toxicity to humans.

Anticancer agent

According to the latest GLOBOCAN Report 2022, an estimated 20 million people were reported to be newly diagnosed with cancer and 9.7 million people lost their lives worldwide in the year 2022.[51] In 2050, cancer incidence is expected to affect up to 35.3 million people.[52] Chemotherapy is one of the leading strategies in cancer treatment. Yet, the effectiveness of chemotherapy is restricted by the lack of specificity and multi-drug resistance of cancer cells.

Nanotechnology is an emerging strategy for bypassing the drawbacks of conventional treatments. ZnO-NPs,

in particular, hold great potential in improving cancer treatment and prognosis. They have been shown to be effective against various types of cancer cells, irrespective of the method of synthesis, as detailed in Table 1. Most importantly, they are reported to be biocompatible[53,54] and demonstrate preferential toxicity towards cancer cells over normal cells.[55] The plausible mechanisms behind the cytotoxicity of ZnO-NPs involve the cellular uptake of ZnO-NPs, followed by release of zinc ions, intracellular ROS generation, loss of mitochondrial potential, activation of pro-apoptotic proteins and down-regulation of anti-apoptotic proteins. This series of reactions subsequently induces cell apoptosis as illustrated in Figure 2.

Interestingly, apart from the known effect of size and concentration, the cytotoxicity of ZnO-NPs is influenced by their synthesis method. Saleemi *et al.*[56] observed superior cytotoxicity in biologically-synthesized ZnO-NPs over chemically-synthesized ZnO-NPs in MCF-7 cells. Within biological synthesis, the choice of plant part is also crucial as stem- and callus-synthesized ZnO-NPs were found to possess equivalent efficacy while leaf-synthesized ZnO-NPs exhibited lower cytotoxicity against A549 cells.[57] Moreover, the cytotoxicity profiles of ZnO-NPs vary depending on their surface chemistry. Doping ZnO-NPs with aluminum and silver remarkedly reduced the growth of MDA-MB-231 and A459 cells, respectively, as compared to the undoped ones.[22,58] Conversely, Cao *et al.*[59] found that lipid-coated ZnO-NPs improved the colloidal stability of ZnO-NPs but were less toxic on HeLa cells as compared to pristine ZnO-NPs. Surface functionalization with surfactants such as polyethylene glycol (PEG), cetyltrimethylammonium bromide (CTAB) and sodium dodecyl sulfate (SDS) has been found to mitigate the ZnO-NPs-induced toxicity.[60] Current studies are still limited at the *in-vivo* stage and have yet to progress to human clinical trials. However, based on extensive studies and developments, ZnO-NPs offer exciting new opportunities and hope for existing cancer treatments.

Drug delivery and targeting

Besides combating bacterial infections and cancer, ZnO-NPs are used for site-specific delivery of bioactive compounds and therapeutic drugs. ZnO-NPs are valued for their non-toxic nature, biocompatibility and versatile, customizable surface chemistry, which allows them to bind, encapsulate and solubilize numerous drugs. By functionalizing the surface of ZnO-NPs with ligands, linker chains and/or markers, ZnO-NPs can improve drug delivery and overcome common shortcomings such as solubility, selectivity, stability and safety.

ZnO-NPs have been used as drug delivery systems for multiple diseases. In the study by Saddik *et al.*[61], azithromycin, an antibiotic, was adsorbed onto the surface of ZnO-NPs for wound healing. The azithromycin-loaded ZnO-NPs demonstrated superior *in-vitro* antibacterial activities and promoted better epidermal regeneration as well as tissue formation in *in-vivo* studies with rat models as compared to azithromycin and ZnO-NPs alone. These observations led to the potential utilization of ZnO-NPs for the effective and rapid healing of infected wounds. On the other hand, Sathishkumar *et al.*[62] reported the utilization of ZnO-NPs to improve the solubility and bioavailability of natural compound, quercetin to cancer cells. The nanocomposite ZnO-quercetin demonstrated remarkable anticancer effect against MCF-7 as compared to ZnO-NPs and quercetin alone. Quercetin release from ZnO-NPs was found to be pH-dependent, faster in pH 5.5 (pH of typical cancer cells) and slower in pH 7.4, suggesting pH-

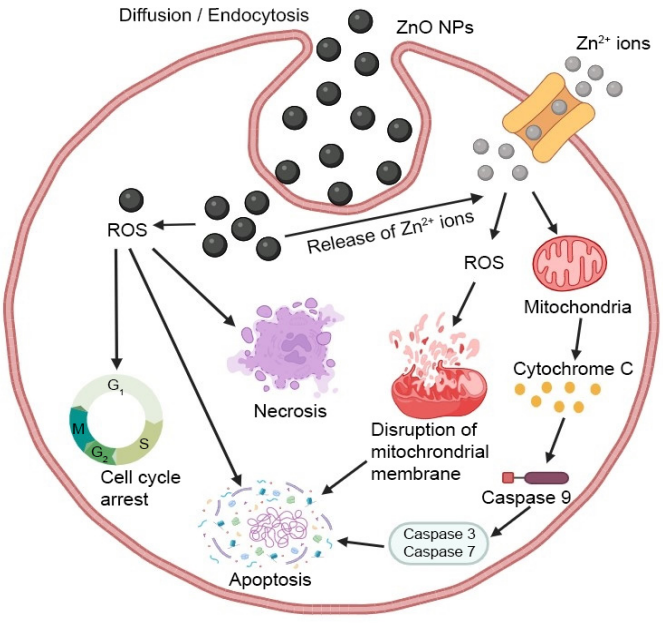

Figure 2. Plausible anticancer mechanisms of ZnO-NPs.

Table 1. Anticancer activity of ZnO-NPs on different cancer cells.

Cancer	Cell lines	Method of synthesis	Shape and size	IC_{50}	Observation	Ref.
Breast	MCF-7	Biological (*Rubus fairholmianus [RF]*)	Spherical 11.3 nm	Not available	RF-ZnO-NPs reduced cellular proliferation and induced cytotoxicity in MCF-7 cells via mitochondria-mediated caspase-dependent apoptotic pathway. Escalation in caspase 3/7 and cytoplasmic cytochrome C along with upregulation of pro-apoptotic proteins (Bax and p53) and downregulation of anti-apoptotic proteins (Bcl-2) were observed.	63
	MCF-7	Biological (*Rhus coriaria L.*)	Spherical and hexagonal 20.5±3.9 nm	35.04-44.86 µg/mL	ZnO-NPs demonstrated concentration-dependent cytotoxicity against MCF-7 and MDA-MB-231 cells. ZnO-NPs triggered cell apoptosis by arresting cells at S-phase and suppressing colony formation. Additionally, the apoptotic markers levels, TP53, BAX and caspase 3 were found to be increased while the expression of Bcl-2 and mesenchymal marker vimentin (VIM) decreased.	64
	MDA-MB-231			55.54-63.71 µg/mL		
	MDA-MB 231	Chemical	225.2 nm	11.23 µg/mL	ZnO-NPs induced dose-dependent toxicity.	65
		Biological (*Colchicine*)	43.7 nm	Not available	Colchicine-ZnO-NPs revealed dose-dependent toxicity and higher reduction in cell proliferation than pure colchicine.	66
Liver	HepG-2	Biological (*Bacillus paramycoides*)	Hexagonal 4.37 nm	57.47 µg/mL	ZnO-NPs revealed profound cell apoptosis against HepG-2 (96%) compared to MCF-7 cells (85%) at the concentration of 1mg/mL. From the *in-vivo* study, ZnO-NPs ameliorated the liver and kidney function profiles of hepatorenal injuries induced by carbon tetrachloride.	67
Oral squamous cell carcinoma	Ca9-22	Commercial	55 nm	17.4 µg/mL	ZnO-NPs induced cell apoptosis via sub-G1 phase arrest, inhibition of p70S6K kinase phosphorylation pathway and activation of caspase cascades via superoxide-induced mitochondrial damage. ZnO-NPs demonstrated selectivity towards gingival squamous cell carcinomas instead of keratinocytes (HaCaT cells). In *an in-vivo* study, ZnO-NPs were able to inhibit tumor growth in the yolk sac of zebrafish inoculated with Ca9-22 cells.	68
	OECM-1			51 µg/mL		
Cervical	HeLa	Biological (*Solanum nigrum leaf*)	Rectangular 30.8–86.8 nm	31.6 µg/mL	ZnO-NPs dose-dependently reduced the viability of HeLa cells. ZnO-NPs caused upregulation of p53, caspase-3 and -9 and downregulated the β-catenin, which is frequently mutated and overexpressed in cancer.	69
Gastric	AGS	Chemical	Sphere 70 nm	8.37±0.93 µg/mL	ZnO-NPs selectively inhibited AGS cells over L929 (healthy) cells via intrinsic apoptosis signaling pathway. It was revealed that ZnO-NPs induced the generation of ROS and subsequently inactivated superoxide dismutase (SOD) and catalase activities, increased caspase-3 and -9 activity and apoptotic mRNA levels (p53, Bax and cytochrome C).	70
Colon	Caco-2	Biological (*Deverra tortuosa*)	Hexagonal 9.3-31.2 nm	50.81 µg/mL	ZnO-NPs showed preferential cytotoxicity towards Caco-2 over A549.	71
Lungs	A549			83.47 µg/mL		
Nerves	SH-SY5Y	Biological (*Clausena lansium (Lour.) Skeels*)	Spherical 24 – 30 nm	15 µg/mL	ROS-mediated autophagy and apoptosis were responsible for the anticancer activity of ZnO-NPs.	72

responsive targeted drug delivery at cancer sites.

Besides, ZnO-NPs are used for the delivery of antidiabetic agents. Hussein *et al.*[73] investigated the efficacy of ZnO-NPs loaded docosahexaenoic acid(DHA) in improving insulin signaling pathways in diabetes mellitus-induced rats. As compared to free DHA, ZnO-NPs-DHA enhanced the insulin signaling pathway by reducing total cholesterol, triglycerides, blood glucose and insulin resistance while increasing the insulin levels. ZnO-NPs have also been employed to modify the efficacy of existing antibacterial drugs through their role as drug delivery agents. Given the length and costly process involved in the discovery of novel antibacterial drugs, enhancing existing drugs serves as a quick, alternative approach to combat the alarming MDR phenomenon. Akbar *et al.*[74] reported the successful conjugation of quercetin, naringin, ceftriaxone, ampicillin and amphotericin B on beta-cyclodextrin (CB) capped ZnO-NPs. The ZnO-NPs-CB-drug complex presented enhanced and substantial antibacterial activities against *Serratia marcescens*, *E.coli* and *P.aeruginosa* compared to their drug counterparts, revealing translational value in the clinical field.

Various ZnO-NPs-based drug delivery systems have been investigated and summarized in Table 2. The plausible mechanisms of ZnO-NPs in drug delivery are depicted in Figure 3. While ZnO-NPs have been exploited in various aspects of healthcare treatment, the current focus is mainly on the delivery of anticancer agents. Exploration of ZnO-NPs as drug delivery systems for other drugs, particularly antibiotics, and for the brain is also of significant interest.

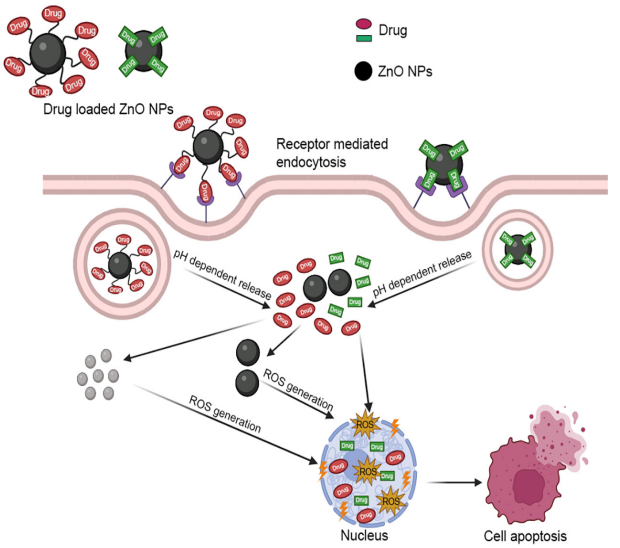

Figure 3. Plausible mechanism for ZnO-NPs as drug delivery agent.

Skin treatment

ZnO-NPs have shown tremendous growth in topical applications. They have been used for different skin conditions; ranging from skin protection to wound care. At present, they are available commercially as over-the-counter products. They are incorporated in personal cosmetics, such as sunscreens for sun-screening effects and in diaper rash creams/ ointments for the treatment of mild skin abrasions and irritations. Due to the positive outcomes from the commercial launchings, ZnO-NPs have been explored in the treatment of skin allergies. For example, Khalaf *et al.*[75] employed nanosized ZnO cream to ameliorate lead oxide (PbO)-induced dermal toxicity. In this study, 1% ZnO cream improved skin lesions, reduced CD4+ and CD8+ T-lymphocytes cells as well as down-regulated intercellular adhesion molecule-1 gene and collagen type 1 gene expression in rats induced with PbO. The results demonstrated the use of ZnO-NPs in alleviating skin allergic dermatitis caused by PbO.

Besides, ZnO-NPs have been extensively exploited to treat acute and chronic wounds. They are included in different types of wound dressings and investigated for wound healing *in-vitro*, *in-vivo* and clinical trials.

Table 2. ZnO-NPs-based drug delivery systems.

Materials	Drug	Cell line / Microorganisms	Ref.
ZnO-NPs	Doxorubicin	A549 (Lungs)	76
ZnO-NPs/ PEG	Doxorubicin	MDA-MB-231 (Breast)	77
ZnO-NPs/ Chitosan	Paclitaxel	MCF-7 (Breast)	78
ZnO-NPs/ Amine	Mupirocin	A431 (Skin)	79
L-histidine/ chitosan / ZnO-NPs/ dialdehyde cellulose hydrogel	Naringenin Quercetin Curcumin	A431 (Skin)	80
ZnO-NPs	Curcumin	Rhabdomyosarcoma; *S.aureus, S. epidermidis, Bacillus cereus* and *E.coli*	81
ZnO-NPs	Metronidazole Clindamycin	*S.aureus*	82
ZnO-NPs/ Amine	Ciprofloxacin	*E.coli, Klebsiella spp, B. subtilis* and *Streptococcus spp*	83
ZnO-NPs	Nanazoxid *Allium sativum*	*Cryptosporidium parvum*	84
Mesoporous ZnO	Natamycin	*Aspergillus fumigatus*	85

In the study by Khorasani *et al.*[86], ZnO-NPs co-loaded with heparin on PVA-chitosan hydrogels demonstrated superior antibacterial activity against *E. coli* and *S. aureus* compared to non-functionalized ZnO-NPs and control and biocompatible as tested on L929 cells. On subsequent testing on male Wistar rats with full-thickness cutaneous wounds, the hydrogels accelerated wound closure, re-epithelization and collagen formation (up to ~90%) by Day 14 with the absence of inflammation. Meanwhile, ZnO-NPs incorporated in quince seed mucilage/chitosan/ polyethylene oxide nano-bandages similarly exhibited biocompatibility and growth inhibition of *S. aureus*.[87] Rapid wound healing with complete skin restoration from grade 2 burn was observed for rats treated with nano-bandages containing ZnO-NPs by Day 21 but not for those nano-bandages without ZnO-NPs.

Efforts have also been directed to load ZnO-NPs onto poly(lactic-co-glycolic acid) (PLGA)/silk fibroin (SF) fabric. PLGA has high biocompatibility, biodegradability and mechanical properties but its hydrophobic nature prevents cell attachment to scaffolds. By blending it with silk fibroin, an ultra-hydrophilic biomaterial with limited mechanical strength, the drawbacks of both materials are balanced out. Majumder *et al.*[88] and Khan *et al.*[89] successfully fabricated PLGA/SF/ZnO-NPs in hydrogels via the sonochemical process and nanofibrous membranes via the electrospinning process respectively. In both studies, the nanocomposite supported cell adhesion and biocompatibility to L929 cells. While Majumder *et al.*[88] demonstrated an 8mm zone of inhibition with *E.coli,* Khan *et al.*[89] revealed that the antibacterial activities of the nanocomposite were concentration-dependent with higher efficiency against *S.aureus* (minimum inhibitory concentration (MIC): 39.06 µg/mL) than *E.coli* (MIC: 78.12µg/mL). A further *in-vivo* study by the latter team using the highest concentration; 3% ZnO-NPs, reported significant wound healing in rats induced with full-thickness cutaneous wounds. The wound contracted by ~86.6% as compared to PLGA/SF (72.0%) and untreated groups (65.2%) in 10 days, along with cellular migration, re-epithelization, collagen deposition and angiogenesis.

Similarly, functionalizing poly(4-hydroxybutyrate) fibrous mats with PEGylated-ZnO-NPs promoted wound healing.[90] The nanocomposite dressing promoted blood clotting and prevented bacterial adhesion by releasing Zn^{2+} ions. *In-vivo* studies on rats' skin defect models and rabbit ear injury models confirmed the dressing's antibacterial and hemostatic properties, respectively. On the other hand, impregnation of ZnO-NPs on sodium alginate/ gum acacia demonstrated the role of nitric oxide (NO) in enhancing wound healing. Increased NO was observed for increased concentration of ZnO-NPs, and an *in-vivo* study with rabbit models demonstrated superior wound diameter reduction in the alginate/ acacia-ZnO-NPs dressings over blank polymer and standard lorexane ointment.[91]

Notable progress of ZnO-NPs in wound care includes the application of calcium alginate-loaded ZnO-NPs dressings on foot ulcers of diabetes mellitus patients.[92] From the randomized clinical trial, patients treated with calcium alginate-ZnO-NPs reported better clinical outcomes than the blank calcium alginate dressings; 75% and 71% wound closure as well as 48 days and 72 days average healing time were reported respectively. A clinical trial with bacterial cellulose/ PVA impregnated with ZnO-NPs has been conducted on patients with post-adrenalectomy.[93] Apart from the analgesic effect, BC/PVA-ZnO-NPs demonstrated a significant wound healing rate of 16.7% (control-silver sulfadiazine: 7.7%), low incidence of adverse reactions (22.2% vs 66.7%) and reduction in dressing frequency.

While many studies have found ZnO-NPs to be safe, careful consideration of their usage still warrants. *In-vivo* dermatological application of ZnO-NPs has been shown to affect hepatic and renal performance[94] and exacerbate UVB-induced keratinocyte damage via autophagy-mediated NLRP3 inflammasome and macrophage exosome secretion.[95] However, ZnO-NPs still represent a promising strategy for managing skin conditions with antibacterial properties.

Antidiabetic agent

Diabetes mellitus (DM) is a chronic metabolic condition defined by elevated blood glucose levels, known as hyperglycemia. It is caused by either insulin resistance or insulin deficiency or both. DM has been associated with zinc dyshomeostasis due to the presentation of enhancement in glycemic control and mitigation of diabetic complications such as neuropathy, cataracts, etc. with zinc supplementation.[96] As ZnO-NPs possess the ability to deliver zinc ions, ZnO-NPs are currently being investigated for the treatment of DM.

Extensive *in-vivo* studies have been performed using ZnO-NPs. In the study by Abdulmalek *et al.*,[97] 10 and 50mg/kg of ZnO-NPs were provided orally to male albino rats that had been induced with diabetes via sequential treatment of high-fat diet and streptozotocin. While ZnO-NPs effectively reduced fasting blood glucose (FBG) and insulin levels during the 6 weeks of treatment, ZnO-NPs concurrently demonstrated improvement in insulin sensitivity, lipid (total cholesterol, high-density lipoprotein and triacylglycerol), liver (alanine transaminase (ALT), aspartate transaminase (AST), and gamma-glutamyl transferase) and kidney (urea and creatine) profiles. ZnO-NPs also counteracted diabetes-induced inflammation and oxidative stress in hepatic and pancreatic tissues as well as prevented weight loss. Most importantly, the team showed the role of ZnO-NPs in modulating insulin signaling pathways in diabetes, activating the AKT pathway and downregulating the MAPK pathway. Similar observations were reported by Elassy *et al.*[98] in diabetic-induced rats given 10 mg/kg/orally/day of ZnO-NPs for 1 month. Although the involvement of AKT and MAPK pathways was not studied, they demonstrated improvement in glucose transporter type 4(GLUT-4) expression and alleviated DM linked-immune suppression through

CD4+ and CD8+ biomarkers within pancreatic cells. Additionally, the restoration of islets of Langerhans and increment of insulin-secreting granules were noticed under transmission electron microscope (TEM) examinations.

DM pathogenesis has also been linked to the dysregulation of microRNAs. microRNAs are important in pancreatic β-cells development and survival, glucose and lipid metabolism as well as insulin production and release. A study by Othman *et al.*[99] found that diabetes-induced rats had significant upregulation of pancreatic microRNAs (miR-24, mir-29a, miR-34a and miR-375) and liver microRNAs (miR-103, mir-107 and miR-34a). Upon treatment with 5mg/kg/body weight/oral ZnO-NPs for 15 consecutive days, these microRNAs' expression significantly decreased compared to untreated diabetic rats. In contrast to the upregulation of the above microRNAs, the liver microRNA (miR-122) was downregulated and ZnO-NPs restored the expression level.

ZnO-NPs have been shown to reduce diabetic complications such as diabetic nephropathy (DN) and diabetic retinopathy (DR). The progression of DN has been associated with the reduction of transcription factor; nuclear erythroid 2–related factor 2 (Nrf-2), which regulates antioxidant response as well as elevation of pro-apoptotic β-cell gene, thioredoxin-interacting protein (TXNIP) and NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. El-Khalik *et al.*[100] found that treatment of DN-induced rats (urinary albumin excretion rate of > 30 mg/24h) with 10mg/kg of ZnO-NPs thrice weekly for 6 weeks restored the redox status. Nrf-2 activity was significantly increased while TXNIP and NLRP3 gene expressions were downregulated. Additionally, ZnO-NPs alleviated histopathological renal changes in which the glomerular basement membrane (GBM) thickened and the number of tubular epithelial cells decreased. At lower dose of ZnO-NPs, attenuation of renal injury was similarly observed.[101] When ZnO-NPs were given at a dose of 2.5mg/kg/daily intraperitoneally for 7 weeks to DN-rats, GBM membrane thickening reduced along with restoration of podocytopenia and foot process width which subsequently resulted in improvement in albuminuria. At the same time, ZnO-NPs were reported to exhibit anti-fibrotic, anti-angiogenic and anti-inflammatory effects in ameliorating the progress of DN. ZnO-NPs mediated renal fibrosis by reducing the expression of collagen IV, pro-fibrotic cytokine (TGF-β1) and fibronectin and increasing the matrix metallopeptidase-9 (MMP-9) while inhibiting abnormal angiogenesis in DN by preventing VEGF-A. As for the anti-inflammatory effect, ZnO-NPs inhibited inflammatory cytokines such as TNF-α, interleukin(IL)-1β and IL-6. On the other hand, Zhang *et al.*[102] reported the repair of altered thickness of retinal, inner nuclear and outer retinal layers in DR-induced rats with 42 days of 10mg/kg/oral ZnO-NPs. In the same study, the level of oxidative stress marker genes (Nrf-2 and HO-1, heme oxygenase-1) and pro-inflammatory markers (procaspase-1, cleaved-caspase-1, IL-1β, IL-18 and ASC, apoptosis-associated speck-like protein containing CARD) was returned to normal. Table 3 summarizes the bottomless applications of ZnO-NPs in diabetes treatment. From these in-depth

Table 3. ZnO-NPs in diabetes treatment.

Materials	Dose	Effects	Ref.
ZnO-NPs	1 mg/mL	ZnO-NPs revealed a comparable drop in blood glucose levels in alloxan-induced diabetic zebrafish as compared to metformin.	103
ZnO-NPs	10 mg or 30 mg/kg/ oral for 30 days	ZnO-NPs dose-dependently reduced the blood glucose and increased the levels of insulin, insulin receptor, GLUT2 and Glucokinase (GCK).	104
ZnO-NPs; ZnO-NPs loaded with DHA	10 mg/kg/body weight/ oral/ day for 30 days	ZnO-NPs and ZnO-NPs/DHA reduced FBG and improved insulin secretion in streptozotocin-induced diabetic rats. ZnO-NPs and ZnO-NPs/DHA increased GLUTs, IRS-1, phosphatidylinositol 3-kinase (PI3K), protein kinase C-α and -γ expression. ZnO-NPs/DHA demonstrated higher activity as compared to ZnO-NPs due to the synergistic effect of ZnO-NPs and DHA.	105
ZnO-NPs with L-carnitine (LC)	10 mg/kg/ intraperitoneal/day of ZnO-NPs with 200mg/ kg/ intraperitoneal of LC for 21 days	Co-treatment of ZnO-NPs with LC improved diabetic injury on the levels of sex hormones (follicle-stimulating hormone, luteinizing hormone, oestradiol, and progesterone) and increased the number of ovarian follicles in streptozotocin-induced diabetic rats, suggesting the role of ZnO-NPs in improving ovulation and fertility in people with diabetes.	106
ZnO-NPs	10 mg/kg/oral/ day for 4 weeks	ZnO-NPs ameliorated functional and histopathological alterations of the kidney in diabetic-induced rats. ZnO-NPs have been reported to activate autophagy by inhibiting the mTOR signaling pathway. ZnO-NPs exerted anti-apoptotic, anti-inflammatory and antioxidant activities, potentially treating diabetic nephropathy.	107
ZnO-NPs and/or pyrazolopyrimidine	10 mg/kg/oral/ day and/or 5 mg/kg/oral/ day for 1 month	ZnO-NPs and/or pyrazolopyrimidine significantly reduced serum glucose and increased serum insulin levels in diabetic-induced rats. A marked increase in hepatic CPT1A and PGC-1 mRNA expression was observed in both ZnO-NPs and/ or pyrazolopyrimidine-treated rats.	108

investigations, apart from treating diabetes, ZnO-NPs are valuable in ameliorating the associated life-quality-robbing complications and may serve as an alternative to current medications.

Antioxidant agent

Endogenous and exogenous ROS are generally modulated by our body's natural antioxidant systems. However, the overproduction of ROS can overwhelm the antioxidant capacity, resulting in oxidative stress and subsequently the development of diseases such as aging, cancer and inflammation.

Various studies have documented the observation of antioxidant activities from ZnO-NPs. They have been found to scavenge free radicals of 2,2-diphenyl-1-picrylhydrazyl (DPPH), superoxide and hydroxyl.[109] Moreover, when ZnO-NPs were administered as dietary supplementation to Japanese quails, ZnO-NPs have been shown to upregulate the mRNA expression of antioxidant enzymes such as SOD, glutathione peroxide (GPX) and catalase in their liver and brain tissues.[110] Interestingly, the antioxidant activities of ZnO-NPs were found to be correlated to their synthesis method. Chemically synthesized ZnO-NPs were found to exhibit diminished or lower radical scavenging activity compared to those biologically synthesized ZnO-NPs (*Azadirachta indica, Hibiscus rosa-sinensis, Murraya koenigii, Moringa oleifera, Tamarindus indica* and *Leucas aspera*).[111,112] The antioxidant activity was suggested to stem from the richness of phytochemicals in plant extracts; flavonoids, phenolics, saponins and carbohydrates. A review of the literature reveals that many studies reporting on the antioxidant activity of ZnO-NPs have utilized the biologically-synthesis approach, as summarized in Table 4. Further studies found that doping plant-synthesized ZnO-NPs with silver resulted in higher scavenging activities compared to undoped ZnO-NPs.[113]

The observation of antio

xidant activities appears to be paradoxical, given that ZnO-NPs are highly recognized as ROS-generating agents. While the antioxidant properties of plant-mediated ZnO-NPs are explainable, the underlying mechanism for the antioxidant activities of pure ZnO-NPs remains to be answered. It is postulated that ZnO-NPs may exhibit dual capabilities in both generating and scavenging ROS. Elevated levels of ROS have been implicated in two distinct roles; 1) induce alteration of nuclear DNA leading to cancer initiation and 2) trigger cancer cell death.[114] If the postulation holds, ZnO-NPs could potentially address both the ROS-triggered pathways.

Diagnostics functionality

Bioimaging

ZnO-NPs are attractive tools in the bioimaging field. They are inexpensive, non-toxic and most importantly, they exhibit luminescent properties. However, their inherent properties limit their direct translation into bioimaging applications. ZnO-NPs, in their pure form, exhibit a wide bandgap at room temperature. This wide bandgap leads to the overlapping of their fluorescence spectra with biological autofluorescence. The bandgap is also located in the UV region which necessitates UV excitation to exhibit fluorescence.[115] UV light is non-suitable in biological imaging because it has low penetration depth and damages biological cells.

To translate ZnO-NPs into useful bioimaging agents, the surface chemistry of ZnO-NPs has been re-engineered and fine-tuned. Functionalization of ZnO-NPs with different materials ranging from organic to inorganic, commonly multiple components, have been performed to achieve desired targeting, dispersion stability, optical and electromechanical properties. Navarro-Palomares *et al.*[116] reported the preparation of amorphous silica shells coated ZnO-NPs, incorporated with fluorescent dye tag; rhodamine B, rhodamine B isothiocyanate or fluorescein for fluorescence imaging. The team utilized a confocal laser microscope to locate the nanoparticles in HeLa cells. From the projected fluorescent images, the modified ZnO-

Table 4. Antioxidant activities of biologically synthesized ZnO-NPs.

Source		DPPH assay (IC_{50})	Other assays (IC_{50})	Ref.
Fruits	*Durio zibethinus* seed	6.39 mg/mL	-	117
	Espresso spent coffee grounds	958.6 µg/mL	-	118
	Olea europeae	87.04 µg/mL	Hydroxyl: 74.05 µg/mL H_2O_2: 55.26 µg/mL Superoxide: 81.37 µg/mL	119
Leaf	*Ailanthus altissima*	78.23 µg/mL	-	120
	Carica papaya	104.9 µg/mL	ABTS: 130.1 µg/mL	121
	Cocos nucifera	764 µg/mL	-	122
	Scoparia dulcis	1.78 µg/mL	-	123
	Sea Lavender (*Limonium pruinosum L. Chaz.) (shoot, leaf and stem)*	86.5 µg/mL	-	124
	Simarouba glauca	410.50 µg/ mL	ABTS: 430.10 µg/mL H_2O_2: 429.80 µg/ mL Superoxide: 485.50 µg/mL	125

NPs were found to be effectively internalized into the cytoplasmic perinuclear region, achieving peak uptake 24h after exposure. The silica coating protected ZnO-NPs from degradation and was substantially stable to reach HeLa cells unaltered. The toxicity study also demonstrated that the modified ZnO-NPs were biocompatible with cell viability of >75% up to 96h. Similarly, Wanas *et al.*[126] reported the functionalization of ZnO-NPs with folic acid and graphene for dual-mode fluorescence imaging of tumors. The graphene/ folic acid-zinc oxide (GN/FA-ZnO) nanocomposite injected into Ehrlich tumor-bearing mice demonstrated bright and clear fluorescence images of the tumor at excitation wavelengths of 400nm and 630nm as depicted in Figure 4(i, ii).

On the other hand, doping techniques have been approached to realize ZnO-NPs' potential as contrast agents in magnetic resonance imaging (MRI). The doping of ZnO-NPs with transition metal elements generates ferromagnetic ZnO-NPs. ZnO-NPs were doped with iron ions (Fe) and functionalized with fucoidan by Nguyen *et al.*[127] for the MRI of atherothrombosis. The prepared Zn(Fe)O-fucoidan NPs demonstrated the capability of detecting the thrombosed area in the rat model of aneurysmal thrombosis. A high-contrast black area was visibly observed in the projected images. These hybrid-coated NPs were low in toxicity and safe for human endothelial cells up to 48h at the dose of 0.1mg/mL. Besides transition metals, efforts have been directed to dope ZnO-NPs with rare-earth elements such as europium[128] and gadolinium.[129] As highlighted by Zangeneh *et al.*,[129] gadolinium-doped ZnO-NPs demonstrated dose-dependent enhancement in MRI and computerized tomography (CT) contrast images as depicted in Figure 4(iii). When compared to untreated cells, gadolinium-doped ZnO-NPs enhanced the images of CT by 1.5 and 2.4-fold and MR by 1.8 and 2.5-fold at 10µg/mL and 20µg/mL respectively, realizing their potential as bioimaging agents.

Contrastingly, Eixenberger *et al.*[130] reported that the physical properties of ZnO-NPs can be altered without surface functionalization and they are yet functional in bioimaging. The team engineered the defect states of ZnO-NPs by manipulating the synthesis variables (amount of polyvinylpyrrolidone, water and annealing temperature). With the reduced bandgap of ~3.1eV, the new ZnO-NPs were found to be sufficiently excited by the 405nm laser of the confocal microscope. Fluorescence spots were observed in treated T47D breast cancer cells without overlapping with biological autofluorescence.

Based on these studies, ZnO-NPs are not flawed by their inherent properties. Intelligent engineering and tuning enable ZnO-NPs to function as bioimagers. To date, the studies on ZnO-NPs as bioimaging agents remain low compared to other applications. Studies on these modified ZnO-NPs require extensive studies as their effect on humans remains questionable.

Biosensor

ZnO-NPs have been extensively investigated for possible use in biosensors due to biocompatibility and possession of an extensive array of potentialities related to tuning and enhancement of their properties. Additionally, ZnO-NPs are valued for their high isoelectric point of ~9.5 which assists in holding negatively charged proteins on surfaces. Up till date, various ZnO-based biosensors have been created to detect proteins, hormones and peptides. For example, silver-doped iron ZnO nanocomposite (Ag@Fe_3O_4/ZnO) deposited on glassy carbon electrode has been used to detect methemoglobin in anemia.[131] The biosensor demonstrated high selectivity and a low detection limit of 0.17µM $HbFe^{3+}$ and stability in 0.1M PBS pH7.4. On the

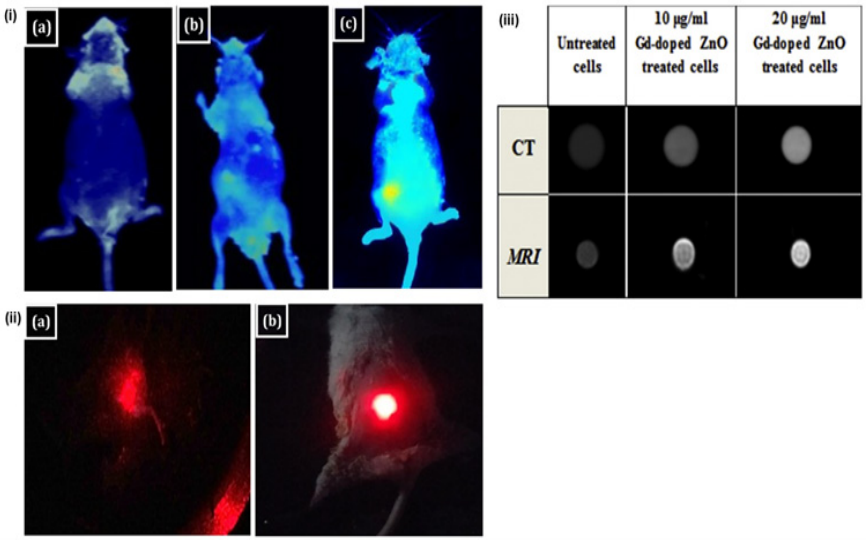

Figure 4. (i) Bioimaging of mice at 400 nm excitation wavelength: (a) Control (b,c) Treated with GN/FA-ZnO nanocomposite; (ii) Bioimaging of mice at 630nm excitation wavelength: (a) Control (b) Treated with 10% GN/FA-ZnO nanocomposite. Reproduced with permission.[126] Copyright 2023, Nature (iii) CT and MRI of untreated and treated SKLC-6 cells with 10 and 20µg/mL gadolinium-doped ZnO-NPs for 24h. Reproduced with permission.[129] Copyright 2019, Elsevier.

other hand, ZnO-nanorods(NRs)/ polydopamine/ glucose oxidase electrode[132] and ZnO/gold nanosquare-array electrode[133] were used in detecting glucose concentration.
Besides detecting biomolecules associated with diseases, ZnO has been used as an immunosensor. Liustrovaite *et al.*[134] reported the preparation of different sizes and morphologies of ZnO nanostructures to detect monoclonal antibodies against prostate-specific antigens (PSA). During the study, the team found that the electrochemical and photoluminescence properties are influenced by the physical properties of the particles. Of the three manufactured ZnO-nanostructures, only rod- (10 - 80 nm) and rod-like spherical (50 - 400nm) nanostructures could be immobilized with PSA for detecting anti-PSA. Further comparison between the two nanostructures showed that rod-like spherical nanostructures offered a 1.75-fold lower limit of detection and quantification of anti-PSA than rod-like nanostructures. Similarly, Thevendran *et al.*[135] utilized ZnO-NRs as a base to create a DNA sensor for acute myeloid leukemia gene mutation. ZnO-NRs were coated in a thin film on interdigitated electrode (IDE) sensor chips, sputtered with gold and immobilized with the ssDNA probe. The biosensor displayed reproducible results (< 5% deviation), high sensitivity with low detection limit of 1 nM as well as good stability over 5 weeks. Most importantly, the biosensor had high selectivity towards unmutated FLT3 genes. Table 5 is a non-exhaustive list of the other applications of ZnO-based biosensors. These numerous studies demonstrated the potential realization of ZnO-based biosensors for the development of health care.

Theranostics functionality

Theranostics, the integration of therapy and diagnosis under a single platform, is a transformative concept in nanomedicine. It involves accurately diagnosing a medical condition through bioimaging and simultaneous delivery of targeted therapy. Theranostics sheds new light on healthcare, explicitly in the field of oncology.

ZnO-NPs have been deemed fit as theranostics agents based on their promising results as it is and as drug delivery agents. Although ZnO-NPs lack intrinsic imaging properties, it has been found that their bandgap and dimensions can be tuned to achieve diagnostics functionality. Engineering of the defect states, doping and coating of their surface are some techniques used for modification. Prasanna *et al.*[136] reported the coating of ZnO-NPs with wider bandgap material, SiO_2, followed by the loading of curcumin. The nanocomposite was found to be hemocompatible and non-toxic to NIH3t3 fibroblast cells. A sustained release of curcumin of 80% in 24h was also recorded. A green fluorescence image was seen when the nanocomposite was put through confocal fluorescence imaging. The study has demonstrated the safety of ZnO-NPs covered with SiO_2 for bioimaging while achieving targeted drug delivery.
In another study, manganese (Mn) doped ZnO-NPs were investigated.[137] Mn doping improved the fluorescence intensity of ZnO-NPs and the intensity increased as Mn doping was added from 1x to 20x. Due to instability and tendency of aggregation, Mn-doped ZnO-NPs were protected with meso-2,3- dimercaptosuccinic acid (DMSA) polymer. The polymer coating reduced the cytotoxicity of Mn-doped ZnO-NPs at the highest dose tested on MCF-7 cells, indicating the potential use of Mn-doped ZnO-NPs in bioimaging. Further conjugation of the surface with epidermal growth factor receptor (EGFR) antibody demonstrated targeted delivery of nanoparticles to cells as evidenced by significantly higher fluorescence intensity of cells as compared to cells treated with only unconjugated nanocomposites. Similarly, Barui *et al.*[138] tuned ZnO-NPs for pancreatic cancer treatment. The team prepared an innovative nanostructure; gadolinium-doped ZnO-NPs, loaded with gemcitabine, coated with extracellular vesicles and Lipo-pep shell and linked to a targeting peptide (CKAAKN). Gadolinium conferred magnetic properties to ZnO-NPs allowing future use in MRI. The nanostructure was observed to have high cell internalization and good

Table 5. ZnO-based nanostructures in biosensor applications.

Composition	Application	Biomarker	Ref.
Chromium/ ZnO-NPs	Electrochemical sensor	Myoglobin (Biomarker of acute myocardial damage)	139
Copper/ ZnO-NPs	Electrochemical sensor	Glucose	140
ZnO/ carbon nano-onion nanocomposite	Electrochemical sensor	Glucose	141
ZnO/ Fe_2O_3 thin nanostructured films	Gas sensor	Nitrogen dioxide (NO_2)	142
Fluorine/ Tin oxide (SnO_2)/ ZnO-NRs/ S protein	Immunosensor	Anti-S protein antibodies (Vaccine-induced antibody)	143
Graphitic carbon nitride (g-C_3N_4)/ ZnO nanocomposite	Immunosensor	*H. pylori* toxin, vacuolating cytotoxin A (VacA)	144
ZnO-NRs/anti-CD5	Immunosensor	Human T-lymphoblast MOLT-4 cells	145
ZnO/ Gold-NPs/ Thiolated tuberculosis probe DNA	DNA biosensor	Mycobacterium tuberculosis DNA	146

cytotoxicity against pancreatic cancer cell lines; BxPC-3 and AsPC-1. The cell viability was 30 – 40% for both cancer cells whereas gemcitabine alone only reduced cell viability to 60%. The other metals that have been studied to leverage the application of ZnO-NPs for theranostics include iron[147] and nickel-ferrite.[148]

While ZnO-NPs have always been the core, Zhang *et al.*[149] demonstrated that ZnO can be used as a shell. Iron oxide was coated with ZnO, followed by immobilization of anti-transferrin receptor (TfR Ab) on the surface and loading of doxorubicin (Fe_3O_4/ZnO/Dox/TfR Ab). The nanocomposite acted as a radiosensitizer in the presence of X-ray irradiation and also provided targeted delivery of doxorubicin to SMMC-7221 cells. Based on non-invasive MRI monitoring, the hepatocellular carcinoma tumor volume of mice was significantly reduced due to the synergistic effect of the nanocomposite and X-ray irradiation. It is important to note from the findings described above that theranostics are appealing due to their multifunctional actions and higher efficacy features than traditional treatments. Figure 5 illustrates the different potential applications of ZnO-NPs in theranostics that could be in the future market for patient usage.

Health Hazards of ZnO-NPs

Despite promising biological advantages, there remain worries regarding the toxicological effects of ZnO-NPs on the human body. Hence, ZnO-NPs have been investigated *in-vitro* and *in-vivo*. The results revealed that when ZnO-NPs are inhaled, injected, or consumed, they express harmful effects on the brain, liver, kidney and reproductive organs.

ZnO-NPs have been reported to induce neurotoxicity. Liu *et al.*[150] revealed the identification of intranasally introduced ZnO-NPs in the rats' olfactory bulb, striatum, hippocampus and cerebral cortex. These ZnO-NPs triggered oxidative stress and inflammatory responses, leading to ultrastructure and cell damage. Upon *in-vitro* studies on neuron-like PC12 cells, ZnO-NPs were shown to destroy the neuronal structure and alter the growth-related protein GAP-43 responsible for the repair and regeneration of neurons and arrest the cell cycle at the G2 phase, leading to decreased cell proliferation. Similarly, ZnO-NPs were found in the mice's brains when exposed intratracheally.[151] Upon intratracheal exposure, ZnO-NPs dose-dependently induced ferroptosis in neuronal cells of mouse cerebral cortex and PC-12 cells through the activation of the c-Jun NH2-terminal kinases (JNK) pathway. The condition was fortunately ameliorable with ferrostatin-1 and deferoxamine, an iron chelator. ZnO-NPs-induced neurotoxicity has been shown to impair cognitive functions related to learning and memory in rats when given biweekly via intraperitoneal.[152] On the other hand, Jin *et al.*[153] found that neurotoxicity contributed to the initiation and development of locomotive defects. Zebrafish larvae developed Parkison diseases-like symptoms when given ZnO-NPs (long NRs) at 50µg/mL and above.

Besides neurotoxicity, ZnO-NPs have been linked to hepatotoxicity. ZnO-NPs exposed rats had liver injury with serum indicators of hepatocyte membrane disruption and cellular efflux after being given ZnO-NPs at 100mg/kg/day/orally for 60 days.[154] A significant increase in alkaline phosphatase (ALP), ALT, AST, total bilirubin and malondialdehyde (MDA) was found along with a reduction of antioxidants, SOD and GPX levels. Histopathological images verified the damages, revealing infiltration of inflammatory cells, hepatocytes necrosis and vacuolar degeneration. In addition to hepatotoxicity, Rahimi *et al.*[155] reported the occurrence of nephrotoxicity in mice. Liver and kidney injury biomarkers (ALT and AST) as well as inflammatory biomarkers (iNOS and TNF-α),

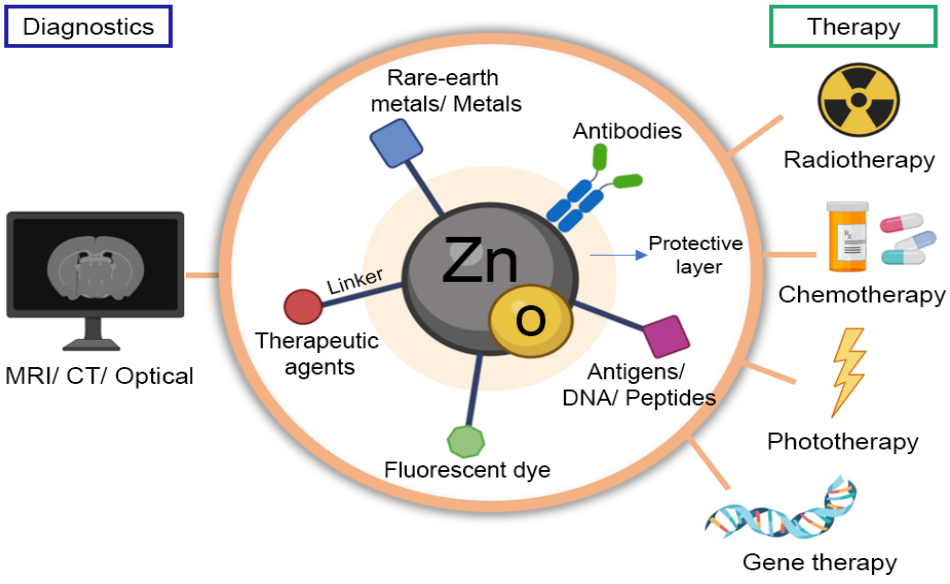

Figure 5. Potential applications of ZnO-NPs in theranostics.

were markedly enhanced while a reduction in creatinine was observed in mice treated orally with 100 and 200 mg/kg/day of ZnO-NPs for 30 days. At the dose of 200 mg/kg, cellular degeneration and necrosis were also observed in both tissues. At low dose of ZnO-NPs (80 µg/kg/thrice weekly for 4 weeks), hepato-renal damage was similarly observed in intraperitoneally treated-rats.[156] In contrast to the above-mentioned toxicity, intraperitoneal ZnO-NPs at 5mg/kg provided renoprotection to rats against cisplatin-induced nephropathy.[157]

The toxicity of ZnO-NPs extends to the reproductive systems.[158-160] ZnO-NPs have been found to disrupt the maturation of mouse ovarian germ cells dose and time-dependently.[161] Irregularly shaped cells indicating necrosis were observed upon 1 day of treatment with ZnO-NPs at 20 and 30 µg/kg and 7 days with 10 µg/kg. Further, decreased cell viability was noticed at the end of 7 days of treatment, irrespective of dose. Moreover, ZnO-NPs demonstrated cytotoxicity towards mouse spermatogonia cells, GC-1. From the *in vitro* results of Pinho *et al.*,[162] ZnO-NPs were toxic to the cells at the dose of 20 µg/mL after 12h of exposure but not at lower doses. Concurrently, alterations in the cytoskeleton and nucleoskeleton were observed. Another notable concern is the effect of ZnO-NPs on embryonic development. ZnO-NPs have been associated with fetotoxicity. Chen *et al.*[163] reported that pregnant mice exposed to 540mg/kg of ZnO-NPs (30nm) had placenta dysfunction, fetal weight loss and fetal growth malfunction. The toxicity was considered size-dependent as Teng *et al.*[164] found that ZnO-NPs of 13nm readily translocated across the intestinal and placenta barrier but not for 57 nm ZnO-NPs. Additionally, ZnO-NPs-induced toxicity is more crucial during the organogenesis phase than the peri-implantation phase. Figure 6 summarizes the potential hazards of ZnO-NPs to humans.

Comparative Performance: ZnO-NPs vs Metal and Other Metal Oxide NPs

ZnO-NPs have been identified as versatile NPs, yet uncertainties persist regarding their performance in comparison to other NPs. Hence, studies have been performed to investigate their relative activities. In Freire *et al.*[165] study,ZnO-NPs and titanium dioxide NPs (TiO_2-NPs) were investigated for their toxicity on A549 cells. Both NPs have been revealed to induce cytotoxicity at 250 µg/mL and 50 µg/mL, respectively. Despite the higher dosage requirement for ZnO-NPs, the effect on cell viability exceeded 50% which was notably higher than the approximately 20% reduction observed in TiO_2-NPs treated cells at the maximum dose tested, 500 µg/mL. Moreover, ZnO-NPs were found to exhibit higher efficiency over copper oxide NPs (CuO-NPs), followed by TiO_2-NPs and tin(IV) oxide NPs (SnO_2-NPs) on human thyroid cancer cells (ML-1).[166] ZnO-NPs and CuO-NPs, identified as the two most efficient NPs, demonstrated IC_{50} values of 22.8 µg/mL and 45.5 µg/mL respectively on ML-1 cells, and IC_{50} values of 68.2 µg/mL and 72.8 µg/mL respectively on rat medullary thyroid carcinoma cells (CA77). Contrary to the commonly argued ROS mechanism, both ZnO-NPs and CuO-NPs were shown to modulate apoptosis via non-ROS mechanisms. When tested on different cancer cell lines, ZnO-NPs similarly portrayed stronger antiproliferative effects than CuO-NPs on MCF-7 cells[167] and aluminum oxide NPs (ANPs) on colon cancer cells (HT29).[168]

In the realm of antimicrobials, ZnO-NPs were shown to be less effective as compared to CuO-NPs[169], silver NPs (Ag-NPs)[170] and magnesium oxide NPs (MgO-NPs).[171] CuO-NPs displayed lower MIC against *S.aureus*, methicillin-resistant *S. aureus* (MRSA), *E.coli* and *Candida albicans* as compared to ZnO-NPs.[169] In the other study by Zeidan *et al.*,[170] Ag/ZnO-NPs coated orthodontic brackets exhibited the highest antibacterial effect followed by Ag-NPs and ZnO-NPs individually coated brackets on *S.mutans* and *Lactobacillus acidophilus (L.acidophilus).* Yet, ZnO-NPs performed better than TiO_2-NPs and calcium oxide NPs (CaO-NPs). ZnO-NPs inhibited the growth of *S.aureus* by

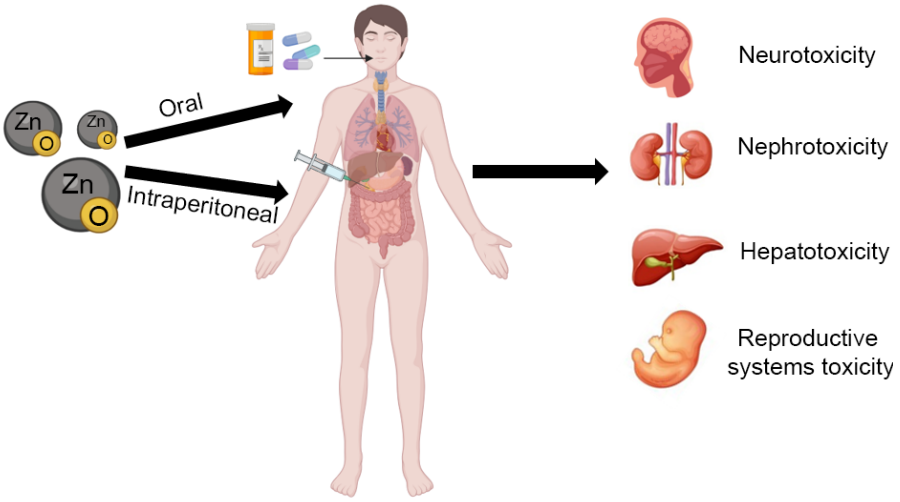

Figure 6. Potential hazards of ZnO-NPs on humans.

66% while TiO_2-NPs and CaO-NPs achieved 56% and 32% respectively.[171] Additionally, ZnO-NPs showcased much lower MIC against *E.coli*, *P.aeruginosa* and *K.pneumonia* of 0.01, 0.02 and 0.01mg/mL respectively while TiO_2-NPs had MIC of 0.04, 0.08 and 0.07mg/mL respectively.[172]

Studies have also evaluated the difference in antioxidant properties between ZnO-NPs and other NPs. ZnO-NPs and CuO-NPs exhibited dose-dependent antioxidant activity, but CuO-NPs exhibited better scavenging potential with IC_{50} of 6.76mg/mL than ZnO-NPs with IC_{50} of 8.99mg/mL.[167] When ZnO-NPs were compared with TiO_2-NPs, ZnO-NPs also had slightly lower antioxidant properties. At 40mg/mL, 53% and 59% radical scavenging activity were observed for ZnO-NPs and TiO_2-NPs respectively.[173] On the other hand, Shanmugan *et al.*[174] demonstrated the antioxidant activity of green-synthesized selenium NPs (Se-NPs) from *Cymbopogon citratus* and *Syzygium aromaticum*, strontium NPs (Sr-NPs) from *Acacia nilotica* and ZnO-NPs from *Cuminum cyminum* and *Syzygium aromaticum*, were similar, in the range of 89.6% to 90.1%. Investigations exploring the comparison between ZnO-NPs and other NPs remain limited, especially considering the vast diversity in their individual structures. Additionally, existing studies predominantly focused on applications such as anticancer, antibacterial and antioxidant. It is hoped that future studies will delve deeper into exploring the comparative effectiveness of ZnO-NPs with different NPs such as bismuth and selenium,[175,176] which have shown promising biomedical prospects and across different biomedical areas soon.

Futuristic Strategies: Heterostructures of ZnO-NPs and 2D Nanomaterials

In recent years, there has been a surge in the discovery of 2D nanomaterials. Dozens of 2D nanomaterials have been reported including black phosphorus, graphene, graphdiyne, transition metal dichalcogenides like molybdenum disulfide (MoS_2) and tungsten disulfide (WS_2) and MXene. 2D nanomaterials are ultrathin, layered structures with highly diverse and tunable mechanical and optoelectronic properties. Despite their relatively recent emergence, these advanced materials expanded swiftly due to their immense potential in biomedical applications such as biosensing, photothermal therapy, photoacoustic imaging, etc.[177-179] Currently, efforts are ongoing to explore the avenues offered by 2D nanomaterials, including their utilization in dimensional-hybrid nanostructures.

Dimensional-hybrid nanomaterials, harnessing the properties and complementing the limitations of both materials, represent an exciting strategy for driving advancements in biomaterial functionality. In the study by Myndrul *et al.*,[180] a non-invasive, stretchable, skin-attachable biosensor device was created, employing ZnO tetrapods decorated with transition metal carbides, MXene (Ti_3C_2Tx) nanoflakes. These nanocomposites were shown to be able to monitor glucose levels via sweat with great sensitivity, low limit of detection and broad detection range of 29 μA mM^{-1} cm^{-2}, ≈ 17 μM and 0.05–0.7 mM respectively. Compared to their individual components, ZnO tetrapods/MXene composites resulted in superior catalytic activity for glucose oxidation in phosphate buffer saline and artificial sweat. Another researcher synthesized MXene/ La^{3+}-doped ZnO/ hemoglobin(Hb) nanocomposite to detect hydrogen peroxide (H_2O_2).[181] H_2O_2 is an important physiological mediator, however, elevated levels of H_2O_2 have been implicated to be the driving force of oxidative stress, cellular damage and disease development. This voltametric sensor displayed a linear array of recognition from 0.2 to 400μM and a sensitivity of 0.08μM in detecting H_2O_2.

Besides MXene, black phosphorus (BP) has been investigated for its potential hybridization with ZnO-NPs, especially for antibacterial applications. The synergistic activities of ZnO-NPs and BP are anticipated to impart effective physical damage to bacteria cells due to their distinct structural morphologies. Moreover, BP possesses a broad bandgap range (0.3 – 2.0 eV), leading to photocatalytic properties and broad optical window absorption under NIR irradiation. This attribute facilitates deep tissue penetration with minimized side effects and heightened bactericidal efficacy as well as accelerates the release of Zn^{2+}. Bose *et al.*[182] showcased that the incorporation of BP/ZnO nanocomposite onto Ti surface-coated bioimplant resulted in enhanced antibacterial effectiveness when compared to BP nanoflakes, notably under the influence of NIR light against *S.aureus* and *E.coli*. The nanocomposite also exhibited negligible toxicity. Similarly, this observation was reported in an electrospun poly (L-lactic acid) membrane incorporated with BP nanosheets/ ZnO.[183]

Other works include the hybridization of ZnO-NPs with MoS_2. Chacko *et al.*[184] successfully prepared a ZnO/ MoS_2 nanocomposite with cytotoxic and anti-angiogenic properties as well as a safety index of ~2. Compared to bare ZnO-NPs and MoS_2, the nanocomposite exhibited significantly lower IC_{50} for HeLa cells and lower xenograft weight. Upon further examination, ZnO-NPs/MoS_2 hindered tumor growth via activation of caspase-3 and suppressed tumor angiogenesis. Graphene oxide (GO)/ ZnO nanocomposite is another area of interest. GO/Ag-doped/ZnO was shown to offer improved bacteriostatic activity against *S.aureus* and *E.coli* as compared to pure ZnO.[185]

As of now, the hybridization of ZnO-NPs with 2D nanomaterials is still in its infancy stage. Several challenges exist, including the complexity of synthesis, time-consuming procedures and issues related to stability. Despite these hurdles, this approach has shown much light in biomedical applications. It is anticipated that further research will be undertaken in the coming years to explore and refine this hybridization approach.

Conclusion

ZnO-NPs synthesized via physical, chemical or biological approach have demonstrated promising applications

across various biomedical fields, including cancer treatment, combating bacterial infections, drug delivery, skin treatments, diabetes management, antioxidant therapy, bioimaging, biosensors and theranostics. ZnO-NPs inhibit the proliferation of cancerous and bacterial cells and promote the bioavailability of therapeutic agents as drug carriers. ZnO-NPs also demonstrated remarkable wound-healing properties attributed to their inherent toxicity against bacterial cells. Besides, they can reduce blood glucose levels, boost insulin production and act as antioxidants. In the realm of diagnostics, ZnO-NPs also exhibit great potential as it is and in combination with therapeutics. Compared to metal and metal oxide NPs, ZnO-NPs were revealed to have superior performance as anticancer agents, albeit with slightly lesser efficacy as antimicrobial and antioxidant agents. To further enhance the effectiveness of ZnO-NPs, the development of heterostructures involving ZnO-NPs with 2D nanomaterials represents a promising strategy.

The applications of ZnO-NPs represent a broadening horizon in diagnosing, treating and preventing various diseases. However, there are concerns with their use that demand further explorations: 1) lack of toxicology study, 2) most studies have been carried out via cell lines and animals and lack progression to human clinical studies and 3) lack of consistency across researchers in terms of preparation procedures and concentrations to be studied. Studies addressing these issues could further elucidate and enhance the understanding of the future use of ZnO-NPs in the biomedical field.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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