APPLICATIONS OF ZnO NANOPARTICLES IN THE BIOMEDICAL FIELD

Abstract

ZnO nanoparticles (NPs) are an appealing research tool in the biomedical sector due to their anticancer and antibacterial capabilities. ZnO NPs' production of reactive oxygen species (ROS) and promotion of apoptosis are responsible for these effects. In addition, ZnO NPs have been effectively used as drug carriers to load and deliver drugs to certain sites, minimizing unwanted toxicity and off-target effects and enhancing synergistic advantages. Here, we go through the characteristics, production methods, and biological uses of ZnO nanoparticles.

Keywords: ZnO, Biomedical Applications, Antibacterial Activity, Biosensor

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I. INTRODUCTION

Nanotechnology has shown to be one of the most flexible and effective technologies for creating medicine delivery systems. Nanomaterials are defined as particles with at least one dimension of 100 nanometers or less. Changes in size and surface modification cause the materials' Physico-chemical properties to vary, making them suitable for biological applications such as medicine delivery, disease diagnosis, and therapy [1]. Four primary types of nanomaterials are often employed in numerous medical applications. Pure metal-based nanoparticles, often known as metal nanoparticles, make up the first class of nanomaterials (e.g., silver, copper, gold, titanium, platinum, zinc, magnesium, iron, and alginate nanoparticles). The other groups of nanomaterials include metal oxide nanoparticles like zinc oxide, titanium dioxide, and others. Examples include the use of Zn-based MOFs, Cu-based MOFs, Mn-based MOFs, AgS, CuS, FeS nanoparticles, Cu-based MOFs, and so forth in a range of medical applications, such as drug delivery and antibacterial activity [2].

Zinc oxide NPs have been praised as potential metal-based nano drugs because of their outstanding potency, biocompatibility, and selectivity. They display thermal and mechanical stability at ambient temperature, as well as broadband gap energy of 3.3 eV and a high excitation binding energy of 60 meV. Zinc oxide NPs have been extensively used in optical, chemical sensing, semiconducting, and piezoelectric research applications [3]. The low toxicity and biodegradability of ZnO nanoparticles are two of its most significant characteristics. Adults require Zn^{2+}, a trace metal that is essential and involved in several metabolic processes. In the US, it is advised that adult males consume 11.0 mg and adult females consume 9.0 mg of Zn^{2+} daily, respectively. Chemically, ZnO has an abundance of -OH groups on its surface, which may easily be functionalized by a variety of surface-decorating substances. ZnO can progressively degrade in both very basic and acidic circumstances, such as those present in tumor cells and the tissue around them if the surface is in close contact with the solution. These desirable characteristics have drawn a lot of interest in ZnO nanoparticles for use in biological applications [4].

1. **Properties of Zinc oxide:** ZnO nanoparticles are one of the cheap materials. These nanoparticles have altered the food industry, agriculture, and medicine distribution [5]. In addition, it is extensively used in the production of photocatalysts, pharmaceuticals, ethanol gas sensors, UV light-emitting devices, and cosmetics [6–10]. These nanoparticles are also used as a sunscreen because of their strong UV light absorption [11]. ZnO nanoparticles offer strong medical applications, including the treatment of diabetes, drug delivery, and cancer [12].

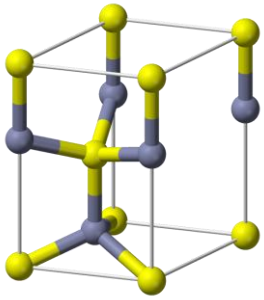

Figure 1: ZnO crystal Structure

They are less hazardous than other metal oxide nanoparticles. Under typical conditions, the crystal structure of crystalline ZnO is wurtzite. It features two (a and c) lattice parameters in addition to a hexagonal unit cell. It belongs in the C46V or P63 mc space group. Figure 1 shows the crystal structure of ZnO's wurtzite. One shows a cation within the central atom, whereas the other shows a cation around the four corner cations. It provides an illustration of a typical sp 3 covalent links for the coordination types [12–15].

2. **Synthesis of ZnO NPs:** The synthesis of nanomaterials can be accomplished using physical, chemical, biological, or hybrid methods. Starting with bulk matter and breaking it down into smaller particles until it reaches nanoscale size is the top-down approach utilized in the physical method. Physical vapor deposition, in which a substance is transferred from a source material (target) to the substrate in the form of vapor particles, laser ablation, in which atoms are removed from a solid through a thermal or non-thermal process with an intense laser beam, and others are a few examples that come to mind.

To create nanomaterials, components are mixed in a wet chemistry process with altered reaction conditions. In this method, sometimes referred to as the bottom-up approach, atoms, molecules or ions in solution first form nucleation, then these species aggregate to create particles that fall within the nano-size range. Due to the ease of the synthesis, this is now the technique of producing nanomaterials that the industry uses most regularly [17]. Some of the technologies used in this method include sol-gel, solvothermal, microwave irradiation, pyrolysis, chemical precipitation, microemulsion, thermal degradation of precursors, etc.

The biosynthesis approach mixes a precursor with microorganisms or plants extracts to produce the required nanomaterial. ZnO nanoparticles have been produced using each of the three aforementioned procedures. For instance, the literature reports on biological techniques utilizing various plant extracts, as well as physical techniques like ball milling [18], physical vapor deposition [19], laser ablation [20], chemical techniques like hydrothermal [21], sol-gel [22], and microemulsion [23], and physical techniques like hydrothermal [21], sol-gel [22], and microemulsion [23].

In the biosynthesis process, the required nanomaterial is produced utilizing a precursor and microorganisms or plant extracts. ZnO NPs have been produced using all three methods. For instance, Table 2 lists a number of the physical, chemical, and biological methods that have been documented in the literature. These methods include ball milling [18], physical vapour deposition [19], and laser ablation [20], as well as hydrothermal [21], sol-gel [22], and microemulsion [23].

A plant extract is any multi-component combination that was created using an appropriate solvent during an extraction procedure. Primary and secondary metabolites are the two major categories used to classify plant-produced compounds. Alkaloids, terpenoids, phenolics, and other secondary metabolites are those that do not contribute to the growth, development, or reproduction of the plant. Nucleic acids, sugars, chlorophyll,

and other substances that are involved in these activities are referred to as primary metabolites.

As a result, extraction entails separating soluble metabolites from the insoluble plant matrix using an appropriate extraction solvent, sometimes known as the menstruum. A variety of methods, such as traditional ones like maceration, decoction, and Soxhlet extraction as well as cutting-edge ones like micro-wave assisted extraction, ultrasound-assisted extraction, and supercritical fluid extraction, are available for the extraction of plants. These methods are covered in reference [26].

It's possible that typical crude extracts were used to synthesize nanomaterials. The extraction method, as described in the cited references, is briefly discussed during the synthesis of ZnO NPs from plant extracts because it affects the composition and concentration of the molecules and because of secondary metabolites in the extract act as reducing and capping agents in the synthesis of nanomaterials. The plant's photochemical components also provide it antioxidant, antibacterial, and other medicinal properties, including the ability to postpone aging, decrease inflammation and prevent certain cancers [27, 28]. These properties are what give the plant its reducing and capping capacities.

3. **Biomedical applications:** The biological uses of ZnO-NPs are now being investigated using a range of materials and chemical synthesis processes, as we have described in this study. Because it is an ecological component and one of nature's inherent minerals, zinc plays a significant role in the metabolism of people, animals, and plants. The biosphere must include levels of zinc that are consistent with the environment since all living things require zinc to exist. ZnO is often utilized for dietary supplements, cosmetic, pharmacological, and medicinal applications [29].

ZnO has piqued attention as a raw material in the pharmaceutical and cosmetic sectors, as a pigment in the paint, concrete, and rubber industries, as a UV filter in products, the textile business, as well as in the realms of medicine and biology [30]. Only the most recent developments in ZnO-NPs for biomedical applications—including drug delivery, gene delivery, anticancer activity, pro-angiogenic property, immunotherapy, antimicrobial activity, wound healing, tissue engineering, treatment for diabetes, bioimaging, and biosensing—are covered in this section. This is a result of the wealth of knowledge on the various applications of ZnO-NPs in biology and medicine. There are several biological uses for ZnO-NPs, which are more fully discussed below in Figure 2.

- **Antidiabetic activity:** Diabetes mellitus is a metabolic disorder marked by inadequate endogenous insulin secretion or activity, which elevates blood sugar levels and causes issues with filtering out the products. Sickness is one of the biggest issues facing the public [31, 33]. Zinc is an important micronutrient that is necessary for numerous biochemical processes, including the metabolism of glucose, and is involved in the production of more than 300 enzymes (Zn). Due to this component's involvement in the signaling route for improved glucose absorption, hepatic glycogenesis is also improved.

Zinc is also necessary for the production, secretion, and signaling of insulin, all of which influence how insulin impacts metabolism. Before the link between zinc and the presence of insulin was identified, it was known that adding zinc made insulin's action persist longer [34–36].

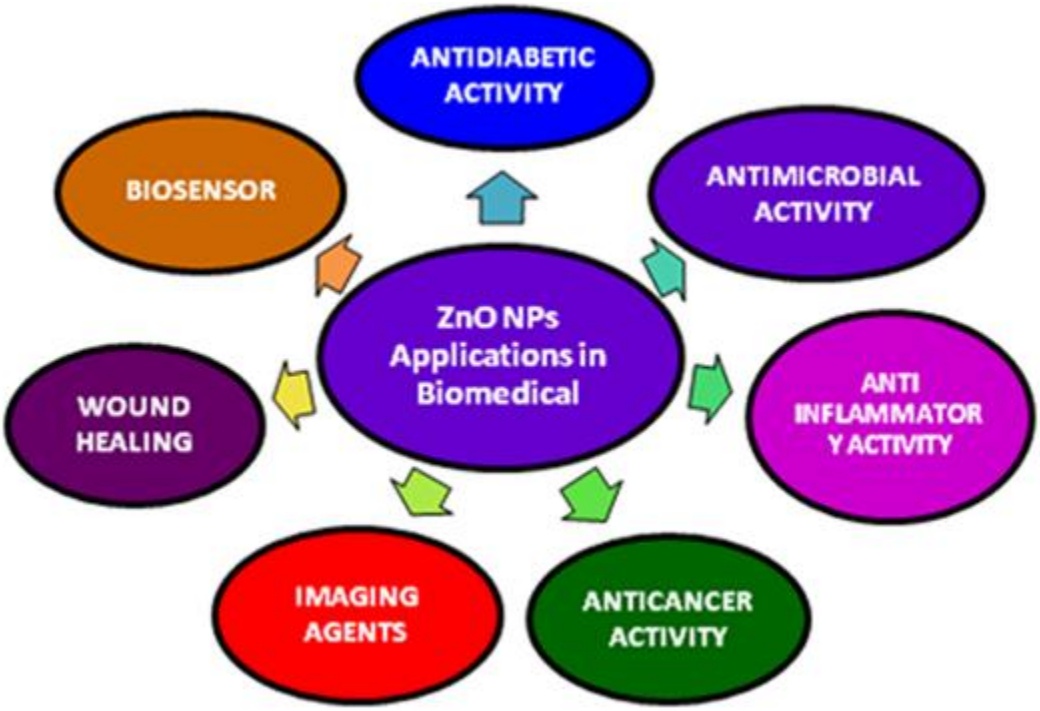

Figure 2: ZnO NPs in Biomedical Applications

As a result, ZnO NPs have been produced as a new agent for zinc administration and have had their antidiabetic potential assessed [37, 38]. Zinc-insulin hexamers specifically improve the structural stability of insulin. By preventing glucose absorption and boosting glucose uptake by skeletal muscle and adipose tissue, zinc also lowers blood glucose levels. Contrary to the length of insulin action, nano zinc compounds with high molecular weight components promote prolonging of hypoglycemic medication activity. Additionally, this type of nanostructure with amphoteric in B, an antifungal medication with systemic activity, lessens the pharmaceutics' nephrotoxic effects [39]. The principles underlying ZnO NPs' anti-diabetic action are as follows: (a) they increase insulin secretion and strengthen the antioxidant defense mechanism in pancreatic -cells; (b) they improve glucose tolerance and lower blood glucose levels; (c) they enhance insulin signaling and sensitivity as well as glucose uptake by the liver, skeletal muscle, and adipose tissue; and (d) they inhibit gluconeogenesis in hepatic. The mechanisms of the antidiabetic action of ZnO NPs are depicted in Fig. 8.

- **Antimicrobial activity:** Because of their tiny size (less than 100 nm) and high surface-to-volume ratio, ZnO nanoparticles interact with bacteria more effectively

than larger particles do. As a result, nanoparticles exhibit more pronounced antibacterial properties. Recent research has demonstrated that these nanoparticles are selectively harmful to bacteria while having little to no impact on human cells [40]. Compared to other nanoparticles from the same elemental family, zinc oxide nanoparticles are more effective against gram-positive bacteria. Salmonella, Staphylococcus aureus, and E. coli infections are increasingly common in ready-to-eat food, which is problematic for food safety and quality. To shield the food from deterioration, antimicrobial substances are added to the packaging.

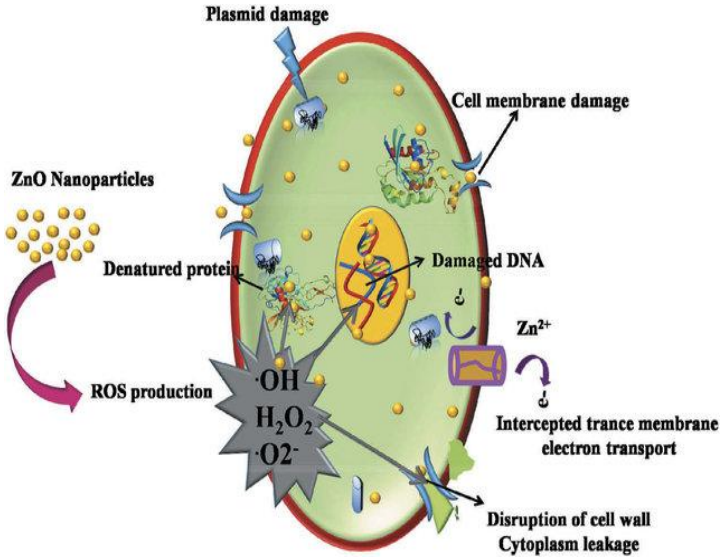

Figure 3: Antimicrobial mechanism

By producing oxidizing species in the form of dioxygen radicals, which are highly reactive and typically react with macromolecules like DNA, enzymes (protein), lipids, etc. [41], reactive oxygen species (ROS) are the most frequent method by which a microbe can be effectively destroyed or at least deactivated. The photoinduced charge carriers (e and h+ pair) are formed when nanomaterials are exposed to a specific amount of radiation, which causes the part to absorb the radiation and e to be expelled from VB to CB [42]. E also reduces oxygen to produce the highly oxidizing dioxygen radical. This method is widely used and efficient against a wide variety of microorganisms at different stages of development.

Metal oxide nanoparticles are the origins of the majority of the metals, which in water produce cationic species. Due to their smaller size and high permeability, these positively charged cations enter cells through the cell membrane and interfere with various metabolic processes by targeting protease enzymes and functionalities like sulfhydryl, amino, and hydroxyl groups, which alter the structure and functionality of the entire molecule. As a result, poisonous compounds or processes are produced, which ultimately prove lethal to the bacterium [43–47].

Since the majority of metallic elements have a positive charge and are electrostatically attracted to the cell wall, membrane dysfunction is a particularly active technique. The critical holes and cavities of cell membranes, which are fragile and semi-permeable, are blocked by the attachment of tiny metal particles. As a result, the transportation and absorption processes are halted, and various cell deformations known as bacteriolysis take place. This causes a variety of bacteria to die quickly [48–51].

- **Anti-Inflammatory Activity:** Inflammation is a complex biological response of the body's tissues to noxious stimuli, such as infections, damaged cells, or irritants. The anti-inflammatory capabilities of ZnO NPs have come to light due to the biological activities of zinc ions and the production of nanoparticles [52]. Zinc oxide NPs have anti-inflammatory effects in response to pathogens or toxins. Inflammation is decreased by zinc oxide nanoparticles (ZNPs) in three different ways: I by blocking the production of pro-inflammatory cytokines like interleukin (IL)-1 and IL-18 by inhibiting NF-kB and caspase 1 in activated mast cells and macrophages; (ii) by inhibiting mast cell proliferation by increasing p53 and reducing the production of thymic stromal lymphopoietin linked to ZnO NPs have been found to have strong anti-inflammatory properties that are not just useful in the treatment of atopic dermatitis [53]. The discovery of nanoparticles provides a new therapeutic avenue for the treatment of illnesses based on inflammation. Due to ZnO NPs' strong reactivity and high surface area to volume ratio, Zn^{+2} ion is easily absorbed by biological membranes [54, 55].

- **Anticancer Activity:** Targeted medication delivery via nanoparticles opens up tremendous possibilities for more safe and efficient cancer therapy. The primary issue impeding the rapid development of cancer therapy techniques is the difficulty of anticancer medications to differentiate between healthy and malignant cells. This is a factor in chemotherapy-related problems and adverse effects [56–58]. ZnO NPs are desirable compared to other nanomaterials because of their low toxicity and biodegradability characteristics. Because zinc is a crucial trace element that controls the activity of several enzymes to maintain homeostasis in the body, ZnO NPs have attracted a lot of interest in the delivery of cancer drugs.

  Additionally, zinc contributes to cellular and humoral immunity, which shields cells from cancer. Via DNA mutation and p53 disruption, zinc efficiency promotes the growth and spread of cancer cells [59,60]. When compared to bulk zinc materials, zinc oxide nanoparticles exhibit enhanced permeability and retention (EPR) effects toward cancer cells, and they can kill cancer cells by producing reactive oxygen species (ROS). Studies on using zinc oxide nanoparticles (NPs) as chemotherapeutic drug delivery methods have also been conducted. Shape, configuration, dispersion grade, and surface charge appear to be significant factors in NP-cytotoxicity in addition to NP-concentration [61]. Additional research on the effects of these values on tumor-killing effectiveness in cancer cells should be conducted. ZnO-NP induces photocatalytic cell death. It has been discovered that zinc oxide nanoparticles may destroy malignant cells with precision. NPs. ZnO NPs can be taken up by cancer cells

via an endocytic pathway; however, the entrance route may vary depending on the cell type. Due to the energy-dependent processes of NP absorption, ZnO NPs are eventually confined to lysosomes, endosomes, and vesicular structures. When lysosomes have an acidic pH, ZnO NPs and Zn2+ ions may be released into the cytosol, selectively eliciting toxicity that results in apoptosis, necrosis, cell cycle arrest, and membrane damage from excessive ROS generation [62, 63].

The mitochondrial electron transport chain is thought to play a role in the formation of intracellular ROS, and it is also thought that cancer-fighting drugs that enter cancer cells may harm the electron transport chain, which would cause a large-scale intracellular release of ROS [64,65]. As a result, increased amounts of ROS cause mitochondrial damage, which is followed by an imbalance in protein activities and, eventually, apoptosis [66]. Because of the elevated intracellular amounts of dissolved zinc ions, increased ROS generation, and subsequent cancer cell death via an apoptotic signaling pathway, ZnO NPs exhibit cytotoxicity in cancer cells [67].

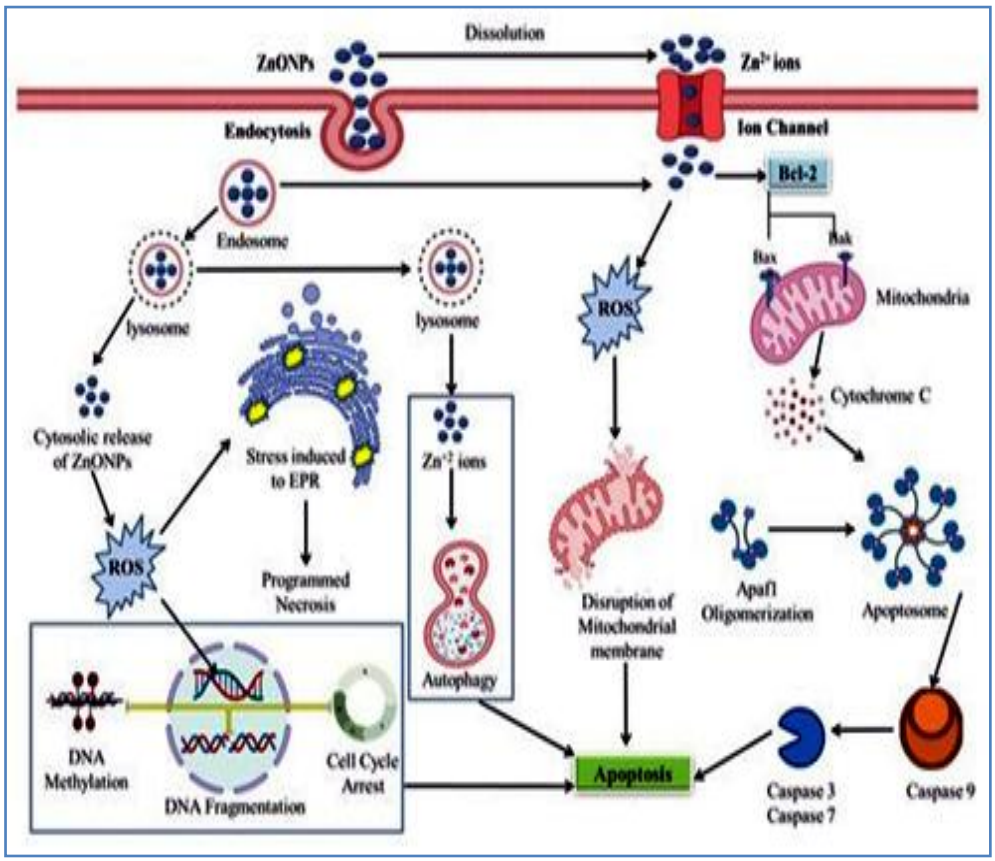

Figure 4: Anticancer Mechanism

Figure 4 shows the probable mechanism behind the anti-cancerous properties of ZnO NPs. ZnO NPs can enter cancer cells by an endocytic pathway, however, the exact mechanism depends on the kind of cell. ZnO NPs are restricted to vesicular structures, endosomes, and ultimately lysosomes by the energy-dependent processes

of NP uptake. Because of the lysosome's acidic pH, ZnO NPs and Zn2+ ions may be released into the cytosol, preferentially producing toxicity that leads to apoptosis, necrosis, cell cycle arrest, and membrane damage because of excessive ROS production. Zn^{2+} ions can also enter cells through ion channels that prevent Bcl-2 indicators from doing their job. This causes Bak/Bax, two pro-apoptotic proteins that enhance cell permeabilization and cytochrome c release, to be produced. The creation of a complex including cytochrome c, apoptotic protease activating factor (Apaf-1), and pro-caspase 9 activates the apoptosome. Caspase 9 activation results in caspase 3 and caspase 7 gene expression and activity, which ultimately induces apoptosis in cancer cells.

4. **Imaging agents:** Due to its accessibility and cost, fluorescence imaging has been widely used in preclinical research [68, 69]. Due to its efficient excitonic blue and near-UV emission, which can also contain green luminescence due to oxygen vacancies, ZnO nanoparticles have been used in several investigations on cellular imaging [70, 71].

   Quantum dots are transparent 10 nm-sized semiconductors known as quantum dots. They possess special optical and electrical characteristics, such as fluorescence when exposed to light sources for bioimaging applications. As a result of ZnO NPs' effective blue and near-UV emissions, which also feature green or yellow luminescence associated with oxygen vacancies, the area of bioimaging is further expanded for this material. The photoluminescent quantum yield of the core emission is increased and protected from photobleaching in core-shell arrangements. QDs have the potential to be employed for imaging and medication delivery in pharmaceutical and biological applications. ZnO nanomaterial is a viable choice for cell imaging and disease research due to its superior intrinsic fluorescence.

5. **Wound healing:** Zinc is a crucial element that aids in the creation of fibrin clots, the control of inflammatory responses, the stimulation of cell proliferation, re-epithelialization, granulation, and angiogenesis, as well as the remodeling of the extracellular matrix[72–74]. ZnO nanoparticles are appealing new therapeutic agents that successfully enter cells, influence the immune system, and encourage infection by giving a sustained supply of zinc to wounds. Numerous investigations on wounds have noted their improved re-epithelization and boosted antibacterial activity. Experimental septic wounds treated with ZnO nanoparticles demonstrated substantial anti-inflammatory and reparative effects.

6. **Biosensors:** Biosensors are useful analytical tools for the targeted detection of various analytes. A bio-selective layer of the biosensor interacts with a specific bio-molecule, and transducers then convert the biological interaction into a physical signal (optical, chemical, electrical, thermal, etc.) [75-77]. The medical field, chemical and biological analysis, environmental monitoring, and the food sector all employ biosensors extensively. When classed according to the detecting principles, they can be photometric, calorimetric, electrochemical, piezoelectric, and more. Due to their special features, nanomaterials, either by themselves or in conjunction with biologically active chemicals,

are gaining more and more interest as a potential platform for the creation of high-performance biosensors.

ZnO nanoparticles also display several advantageous properties for bio-sensing, including high catalytic efficiency, robust adsorption capacity, and high isoelectric point, which are appropriate for the electrostatic adsorption of certain proteins. They are also potential nanomaterials for biosensors used to encapsulate various bio-molecules such as enzymes, antibodies, and other proteins due to their large surface area, strong biocompatibility/stability, low toxicity, and high electron transfer capacity. Most ZnO-based biosensors have been reported to be used for the detection of several small molecule analytes, including glucose, phenol, H2O2, cholesterol, urea, etc. For the detection of gases and biochemicals, zinc oxide nanoparticles have been employed as biomedical diagnostic/analytical sensors. The pore characteristics of gas sensors play a crucial role in ensuring optimal adsorption performance by allowing adsorbates into interior surfaces. For instance, ethanol and acetone may be swiftly and precisely detected by very sensitive and selective ZnO nanowires/NPs gas sensors [77-81].

II. CONCLUSION AND FUTURE WORK

In the previous few decades, nanotechnology has made enormous strides and had a revolutionary influence on biomedicine. Nanomaterials can display features that are different from both molecules and bulk solids when they are less than a few hundred nm, which is many orders of magnitude smaller than human cells. One of the most important microelements, needed for crucial processes, is zinc. The majority of the zinc that is ingested by the body through food and water is absorbed in the small intestine, where it is subsequently transferred to the blood plasma, where albumins and globulins bind it, or to the tissues, where it is stored in proteins that accumulate zinc and cadmium. Zinc is a component of both hormone complexes and metalloenzymes.

Due to its nano size, optical, chemical, biological, and pharmacological characteristics, zinc and its compounds can lead to a wide range of biomedical applications. Due to the potential to control the functional activity of muscles using zinc ions in both normal and diseased situations, the study in this area is especially important from a practical standpoint. Depending on the production methods, zinc oxide NPs can have a variety of physicochemical properties. With their anticancer, antidiabetic, antibacterial, anti-inflammatory, and wound healing properties, they have remarkable promise as treatments. Biosensors and imaging devices both employ zinc oxide nanoparticles (NPs). It is anticipated that ZnO NPs would soon be widely used in both non-clinical and clinical investigations as novel therapeutic agents. Due to its extensive action against both Gram-positive and Gram-negative bacteria, ZnO in nanoparticle form is a potential antibacterial agent; nevertheless, the precise mechanism of ZnO NPs is not fully understood. Porous network architectures may improve the performance of synthetic ZnO NPs, which may be arranged into one, two, and three-dimensional structures. As a result, researching it in depth offers many valuable theoretical and practical applications. We anticipate that ZnO NPs will be investigated in the future as antibacterial agents for mouthwashes, lotions, and ointments.

REFERENCES

[1] MostafaMobrouk, Rajakumarirajendran, Islam e.Soliman, Mohamed M.Ashour, Hanan H Beherei, KhairyM.Tohamy, Sabu Thomas, NandakumarKalarikkal, Gangasalam Arthanareeswaran, andDigantaB.Das, "Nanoparticle and nanoporous membrane Mediated Delivery of Therapeutics", Pharmaceutics 2019, 11, 294.

[2] Asim Ali Yaqoob, Hilal Ahmad, TabassumParveen, Akil Ahmed, Mohammed Oves, Iqbal. I.Ismail, Huda A. Qari, Khalid Umar, Mohamad Nasir Mohammad Ibrahim, "Recent Advances in Metal Decorated Nanomaterials and Their Various, Biological Applications: A Review", "Frontiers Chemistry,2020.

[3] Eon Jin, Hyo-Eon Jin, "Synthesis, Characterization, and Three-Dimensional Structure Generation of Zinc Oxide- Based Nanomedicine for Biomedical Applications", Pharmaceutics, 2019,11, 575.

[4] Yin Zhang, Tapas R.Nayak, Hao Hong, Weibo, " Biomedical Applications of Zinc Oxide Nanomaterials", CurrMol Med, 2013,13(10):1633-1645.

[5] Mirzaei, H. and Darroudi, M., "Zinc Oxide Nanoparticles: Biological Synthesis and Biomedical Applications." Ceramics Inter., 2017, 43, 907–914.

[6] Zheng, Z. Q., Yao, J. D., Wang, B. and Yang, G. W., "Light-Controlling, Flexible and Transparent Ethanol Gas Sensor Based on ZnO Nanoparticles for Wearable Devices." Sci. Rep., 2015, 5, 11070.

[7] Liu, K. K., Shan, C. X., Zhou, R., Zhao, Q. and Shen, D. Z., "Large-Scale Synthesis of ZnO Nanoparticles and their Application as Phosphors in Light-Emitting Devices."Optical Mater. Exp., 2017, 7, 2682–2690.

[8] Sridar, R., Ramanan, U. U., and Rajasimman, M., "ZnO Nanoparticles–Synthesis, Characterization and its Application for Phenol Removal From Synthetic and Pharmaceutical Industry Wastewater." Environ. Nanotechnol.Monit. Manag., 2018, 10, 388–393.

[9] Gnanasekaran, L., Hemamalini, R., Saravanan, R., Ravichandran, K., Gracia, F., Agarwal, S. and Gupta, V. K., "Synthesis and Characterization of Metal Oxides (CeO2, CuO, NiO, Mn3O4, SnO2, and ZnO) Nanoparticles as Photo-Catalysts for Degradation of Textile Dyes." J.Photochem. Photobio. B: Biology, 2017,173, 43–49.

[10] Subramaniam, V. D., Prasad, S. V., Banerjee, A., Gopinath, M., Murugesan, R., Marotta, F., Sun, X. F. and Pathak, S., "Health Hazards of Nanoparticles: Understanding the Toxicity Mechanism of NanosizedZnO in Cosmetic Products." Drug Chem. Toxicol., 2019, 42, 84–93.

[11] Wright, P. F., "Realistic Exposure Study Assists Risk Assessments of ZnO Nanoparticle Sunscreens and Allays Safety Concerns." J. Invest. Dermatol., 2019, 139,277–278.

[12] Bisht, G. and Rayamajhi, S., "ZnONanoparticles: A Promising Anticancer Agent." Nanomedicine, 2016, 3, 9.

[13] Yang, X., Zhang, C., Li, A., Wang, J. and Cai, X., "Red Fluorescent ZnO Nanoparticle Grafted with Polyglycerol and Conjugated RGD Peptide as Drug Delivery Vehicles for Efficient TargetCancer Therapy." Mater. Sci, Engg., C,2019, 95, 104–113.

[14] Da Silva, B. L., Caetano, B. L., Chiari-Andréo, B. G., Pietro, R. C. L. R. and Chiavacci, L. A., "Increased Antibacterial Activity of ZnO Nanoparticles: Influence of Size and Surface Modification." Colloids Surf. B, Biointerf., 2019, 177,440–447.

[15] San Tang, K., "The Current and FuturePerspectives of Zinc Oxide Nanoparticle in the Treatment of Diabetes Mellitus." Life Sci., 2019, 239, 117011.

[16] S. Hashmi, Comprehensive materials processing, Newnes, 2014.

[17] P. Iqbal, J.A. Preece, P.M. Mendes, Nanotechnology: The "Top-Down" and "Bottom-Up" Approaches, Supramol. Chem. (2012) 1–14.

[18] N. Salah, S.S. Habib, Z.H. Khan, A. Memic, A. Azam, E. Alarfaj, N. Zahid, S. Al-Hamedi, High-energy ball milling technique for ZnO nanoparticles as antibacterial material, Int. J. Nanomedicine 6 (2011) 863.
[19] H. Kim, W. Sigmund, ZnO nanocrystals synthesized by physical vapor deposition, J. Nanosci. Nanotechnol. 4 (2004) 275–278.
[20] N. Mintcheva, A.A. Aljulaih, W. Wunderlich, S.A. Kulinich, S. Iwamori, Laser-ab-latedZnO nanoparticles and their photocatalytic activity toward organic pollutants, Materials 11 (2018) 1127.
[21] S. Mishra, R. Srivastava, S. Prakash, R. Yadav, A. Panday, Photoluminescence and photoconductive characteristics of hydrothermally synthesized ZnO nanoparticles, Opto-Electron. Rev. 18 (2010) 467–473.
[22] J.N. Hasnidawani, H.N. Azlina, H. Norita, N.N. Bonnie, S. Ratim, E.S. Ali, Synthesis of ZnO nanostructures using sol-gel method, Procedia Chem. 19 (2016),211–216.
[23] M. Inoguchi, K. Suzuki, K. Kageyama, H. Takagi, Y. Sakabe, Monodispersed and well-crystallized zinc oxide nanoparticles fabricated by microemulsion method, J. Am. Ceram. Soc. 91 (2008) 3850–3855.
[24] S. Küünal, P. Rauwel, E. Rauwel, Plant extract mediated synthesis of nanoparticles, in Emerging Applications of Nanoparticles and Architecture Nanostructures, Elsevier, 2018, pp. 411-446.
[25] J.N. Kabera, E. Semana, A.R. Mussa, X. He, Plant secondary metabolites: biosynthesis, classification, function and pharmacological properties, J. Pharm.Pharmacol. 2 (2014) 377–392.
[26] J. Azmir, I. Zaidul, M. Rahman, K. Sharif, A. Mohamed, F. Sahana, M. Jahurul, K. Ghafoor, N. Norulaini, A. Omar, Techniques for extraction of bioactive compounds from plant materials: a review, J. Food Eng. 117 (2013) 426–436.
A. Altemimi, N. Lakhssassi, A. Baharlouei, D.G. Watson, D.A. Lightfoot, Phytochemicals: extraction, isolation, and identification of bioactive compounds from plant extracts, Plants 6 (2017) 42.
[27] L. Mahlaule-Glory, Z. Mbita, B. Ntsendwana, M. Mathipa, N. Mketo, N. Hintsho-Mbita, ZnO nanoparticles via Sutherlandiafrutescens plant extract: physical and biological properties, Mater. Res. Express 6 (2019) 085006.
[28] Jinhuan Jiang, Jiang Pi, JiyeCai, " The Advancing of Zinc Oxide Nanoparticles for Biomedical Applications", "Bioinorganic Chemistry and Applications", 2018, doi.org/10.1155/2018/1062562.
[29] Fahadulislam, Sheikh Shohag, Md.Jalaluddin, Md. Rezaul Islam, Mohamed H.Nafady, AklimaAkter, SAikatMitra, Arpita, Talha Bin Emran, SimonaCavalu, " Exploring the Journey of Zinc Oxide Nanoparticles (ZnO-NPs) toward Biomedical Applications", " Materials (Basel).
[30] Alkali A., Abdelazim A.M., Afifi M. Antidiabetic activity of zinc oxide and silver nanoparticles on streptozotocin-induced diabetic rats. Int. J. Mol. Sci. 2014;15:2015–2023.
[31] Ahmed F., Husain Q., Ansari M.O., Shadab G.G.H.A. Antidiabetic and oxidative stress assessment of bio-enzymatically synthesized zinc oxide nanoformulation on the streptozotocin-induced hyperglycemic mic. Appl. Nanosci. 2020;10:879–893.
[32] El-Gharbawy R.M., Emara A.M., Abu-Risha S.E. Zinc oxide nanoparticles and a standard antidiabetic drug restore the function and structure of beta cells in Type-2 diabetes. Biomed. Pharmacother. 2016;84:810–820. DOI: 10.1016/j.biopha.2016.09.068.
[33] Nazarizadeh A., Asri-Rezaie S. Comparative Study of Antidiabetic Activity and Oxidative Stress Induced by Zinc Oxide Nanoparticles and Zinc Sulfate in Diabetic Rats. AAPS Pharm. Sci. Tech. 2016;17:834–843.
[34] Wahba N.S., Shaban S.F., Kattaia A.A.A., Kandeel S.A. Efficacy of zinc oxide nanoparticles in attenuating pancreatic damage in a rat model of streptozotocin-induced diabetes. Ultrastruct. Pathol. 2016;40:358–373.

[35] Amiri A., Dehkordi R.A.F., Heidarnejad M.S., Dehkordi M.J. Effect of the Zinc Oxide Nanoparticles and Thiamine for the Management of Diabetes in Alloxan-Induced Mice: A Stereological and Biochemical Study. Biol. Trace Elem. Res. 2018;181:258–264.
[36] Rehana D., Mahendiran D., Kumar R.S., Rahiman A.K. In vitro antioxidant and antidiabetic activities of zinc oxide nanoparticles synthesized using different plant extracts. Bioprocess Biosyst. Eng. 2017;40:943–957.
[37] Asani S.C., Umrani R.D., Paknikar K.M. Differential dose-dependent effects of zinc oxide nanoparticles on oxidative stress-mediated pancreatic β-cell death. Nanomedicine. 2017;12:745–759.
[38] Sharma, R.K.; Ghose, R. Synthesis of zinc oxide nanoparticles by homogeneous precipitation method and its application antifungal activity against Candida Albicans. Ceram. Int. 2015, 41, 967–975.
[39] Taufiq, A.; Ulya, H.N.; Utomo, J.; SunaryonoHidayat, N.; Susanto, H.; Mufti, N.; MunasirSoontaranon, S. IOP Conference Series.J. Phys. 2018, 1093, 012001.
[40] Singh, B.R. Evaluation of Antibacterial Activity of Salvia Officinalis L. Sage Oil on Veterinary Clinical Isolates of Bacteria. Medicine 2013, 11–27.
[41] Methods for the determination of susceptibility of bacteria to antimicrobial agents. Terminal. Clin.Microbiol. Infect. 1998, 4, 291–296.
[42] Rampersad, S.N. Multiple Applications of Alamar Blue as an Indicator of Metabolic Function and Cellular Health in Cell Viability Bioassays. Sensors 2012, 12, 12347–12360.
[43] Elshikh, M.; Ahmed, S.; Funston, S.; Dunlop, P.; McGaw, M.; Marchant, R.; Banat, I.M. Resazurin-based 96-well plate method for the determination of the minimum inhibitory concentration of biosurfactants. Biotechnol. Lett. 2016, 38, 1015–1019.
[44] Padiyara, P.; Inoue, H.; Sprenger, M. Global Governance Mechanisms to Address Antimicrobial Resistance. Infect. Dis. Res. Treat. 2018, 11, 1–4.
[45] Patil, M.; Poyil, A.N.; Joshi, S.D.; Patil, S.A.; Patil, S.A.; Bugarin, A. Synthesis, molecular docking studies, and evaluation of new structurally diverse areas. Bioorganic Chem. 2019, 87, 302–311.
[46] Toche, R.B.; Janrao, R.A. Synthesis, characterization and antimicrobial evaluation of novel urea, sulfonamide and acetamide 3,4-dihydropyrazino[1,2-a]indol-1(2H)-one derivative. Arab. J. Chem. 2019, 12, 3406–3416.
[47] Patil, P.P.; Meshram, J.V.; Bohara, R.A.; Nanaware, S.G.; Pawar, S.H. ZnO nanoparticle-embedded silk fibroin–polyvinyl alcohol composite film: A potential dressing material for infected wounds. New J. Chem. 2018, 42, 14620–14629.
[48] Karton-Lifshin N, Segal E, Omer L, Portnoy M, Satchi-Fainaro R. A unique paradigm for a Turn-ON near-infrared cyanine-based probe: noninvasive intravital optical imaging of hydrogen peroxide. J Am Chem Soc. 2011;133(28):10960-10965.
[49] Guo Z, Park S, Yoon J, Shin I. Recent progress in the development of near-infrared fluorescent probes for bioimaging applications. ChemSoc Rev. 2014;43(1):16-29.
[50] Awad A, Abou-Kandil AI, Elsabbagh I, Elfass M, GaafarM.Polymer nanocomposites part 1: Structural characterization of zinc oxide nanoparticles synthesized via novel calcination method. J Thermoplast Compos 2015;28(9):1343-1358.
[51] Gunalan G, Vijayalakshmi K, Saraswathy A, Hopper W, Tamilvannan T. 2014. Anti-
[52] Inflammatory activities of phytochemicals from bauhinia variegata Linn. Leaf: An in silico approach. Journal of Chemical and Pharmaceutical Research 6: 334–348.
[53] Mueller M, Hobiger S, Jungbauer A. 2010. Anti-inflammatory activity of extracts from fruits, herbs, and spices. Food Chemistry 122: 987–996.
[54] Ilves M, Palomäki J, Vippola M, LehtoM,Savolainen K, Savinko T, Alenius H. 2014.
[55] Topically applied ZnO nanoparticles suppress allergen-induced skin inflammation but induce vigorous IgE production in the atopic dermatitis mouse model. Particle and Fibre Toxicology 11: 38

[56] Macrophages RAW, Kim M, Jeong H. 2015. zinc oxide Nanoparticles Suppress LPS-Induced NF- B Activation by Inducing A20, a negative regulator of NF-KB, in RAW264.7Macrophages. NanoscienceandNanotechnology 15: 6509–6515.
[57] R.J. Carmody, T.G. Cotter, Signaling apoptosis: a radical approach, Redox Rep. 6(2001) 77–90.
[58] C. Hanley, J. Layne, A. Punnoose, K.M. Reddy, I. Coombs, A. Coombs, K. Feris, D.
[59] Wingett, Preferential killing of cancer cells and activated human T cells using zinc oxide nanoparticles, Nanotechnology 19 (2008) 295103–295113.
[60] H. Wang, D. Wingett, M.H. Engelhard, K. Feris, K.M. Reddy, P. Turner, J. Layne, C.Hanley, J. Bell, D. Tenne, C. Wang, A. Punnoose, Fluorescent dye encapsulated ZnO particles with cell-specific toxicity for potential use in biomedical applications, J.Mater. Sci. Mater. Med. 20 (2009) 11–22.
[61] E.A. Murphy, B.K. Majeti, L.A. Barnes, M. Makale, S.M. Weis, K. Lutu-Fuga, W.Wrasidlo, D.A. Cheresh, Nanoparticle-mediated drug delivery to tumor vasculature suppresses metastasis, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 9343–9348.
[62] C.H. Kuo, H.H. Michael, Morphologically controlled the synthesis of Cu2O nanocrystals and their properties, Nano Today 5 (2010) 106–116.
[63] Y. Zhang, W. Chen, S.P. Wang, Phototoxicity of zinc oxide nanoparticle conjugates in human ovarian cancer, J. Biomed. Nanotechnol. 4 (2008) 432–438.
[64] P.J. Moos, K. Chung, D. Woessner, M. Honeggar, N.S. Cutler, J.M. Veranth, ZnOpartic ulate matter requires cell contact for toxicity in human colon cancer cells, Chem.Res. Toxicol. 23 (2010) 733–739.
[65] D.B. Warheit, T.R. Webb, K.L. Reed, S. Frerichs, C.M. Sayes, Pulmonary toxicity study in rats with three forms of ultrafine-TiO2 particles: differential responses related to surface properties, Toxicology 230 (2007) 90–104.
[66] Stowe, D.F.; Camara, A.K. Mitochondrial reactive oxygen species production in excitable cells: Modulators of mitochondrial and cell function. Antioxid. Redox Signal.**2009**, 11, 1373–1414.
[67] Moghimipour, E.; Rezaei, M.; Ramezani, Z.; Kolchak, M.; Amini, M.; Angali, K.A.; Dorkoosh, F.A.; Handali, S. Transferrin targeted liposomal 5-fluorouracil induced apoptosis via mitochondria signaling pathway in cancer cells. Life Sci.**2018**, 194, 104–110.
[68] Guo, C.; Sun, L.; Chen, X.; Zhang, D. Oxidative stress, mitochondrial damage, and neurodegenerative diseases. Neural Regen. Res.**2013**, 8, 2003.
[69] Jiang, J.; Pi, J.; Cai, J. The advancing of zinc oxide nanoparticles for biomedical applications. Bioinorg. Chem. Appl. 2018, 2018, 1062562.
[70] Huang X, Lee S, Chen X. Design of "smart" probes for optical imaging of apoptosis. Am J Nucl Med Mol Imaging. 2011;1:3–17.
[71] Wang RE, Niu Y, Wu H, Amin MN, Cai J. Development of NGR peptide-based agents for tumor imaging. Am J Nucl Med Mol Imaging. 2011;1:36–46.
[72] Heo YW, Norton DP, Pearton SJ. Origin of green luminescence in ZnO thin film grown by molecular-beam epitaxy. J Appl Phys. 2005;98:073502–6.
[73] Vanheusden K, Warren WL, Seager CH, et al. Mechanisms behind green photoluminescence in ZnO phosphor powders. J Appl Phys. 1996;79:7983–90.
[74] Stowe, D.F.; Camara, A.K. Mitochondrial reactive oxygen species production in excitable cells: Modulators of mitochondrial and cell function. Antioxid. Redox Signal.**2009**, 11, 1373–1414.
[75] Moghimipour, E.; Rezaei, M.; Ramezani, Z.; Kolchak, M.; Amini, M.; Angali, K.A.; Dorkoosh, F.A.; Handali, S. Transferrin targeted liposomal 5-fluorouracil induced apoptosis via mitochondria signaling pathway in cancer cells. Life Sci.**2018**, 194, 104–110.
[76] Guo, C.; Sun, L.; Chen, X.; Zhang, D. Oxidative stress, mitochondrial damage, and neurodegenerative diseases. Neural Regen. Res.**2013**, 8, 2003.
[77] Jiang, J.; Pi, J.; Cai, J. The advancing of zinc oxide nanoparticles for biomedical applications. Bioinorg. Chem. Appl. 2018, 2018, 1062562.

[78] C. Clark, C. Lyons, Electrode systems for continuous monitoring in cardiovascular surgery. Ann N Y AcadSci 102 (1962) 29–45.
[79] D.C. Turner, C.Y. Chang, K. Fang, S.L. Brandow, and D.B. Murphy, Selective adhesion of functional microtubules to patterned silane surfaces, Biophysical Journal 69(6) (1995),2782–2789.
[80] F.W. Scheller, U. Wollenberger, A. Warsinke, F. Lisdat, Research and development in biosensors. CurrOpinBiotechnol 12 (2001) 35–404.
[81] N. Nath and A. Chilkoti, A colorimetric gold nanoparticle sensor to interrogate biomolecular interactions in real-time on a surface, Analytical Chemistry 74(3) (2002) 504–509.
[82] N.M. Ravindra, C. Prodan, Advances in the Manufacturing, Types, and Applications of Biosensors, (2007) JOM 37-43.
[83] S.H. North, E.H. Lock, Critical aspects of biointerface design and their impact on biosensor development, Anal BioanalChem (2010) 397:925–933.

