ROLE OF ZnO NANOPARTICLES AS A NOVAL FORMULATION

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ABSTRACT

ZnO nanoparticles are presently used in a variety of fields, including tissue engineering, cancer therapy, biosensing, drug and gene delivery, nanomachines that may mimic biological processes, and shape-memory polymers used in molecular switches, among others. In the pharma industry ZnO nanoparticles have various applications and biomedical applications like antibacterial, antimicrobial, antifungal, anti-inflammatory, antidiabetic, antiproliferative activities, anticancer effects, treatment of different skin diseases, drug carrier and bioimaging. Laser ablation, hydrothermal processes, electrochemical depositions, sol-gel chemical vapour deposition, thermal decomposition, combustion processes, ultrasound, microwave-assisted combustion method, two-step mechanochemical-thermal synthesis, anodization, co-precipitation, electrophoretic deposition, and precipitation using solution concentration, pH, and washing medium are some potential methods for producing ZnO nanoparticles. ZnO has a strong optical absorption in the UVA (315–400 nm) and UVB (280–315 nm) areas, which is advantageous in the antibacterial response and utilized as a UV protector in cosmetics. ZnO nanoparticles have various biomedical applications such as: anticancer, antibacterial, antimicrobial, anti-inflammatory antioxidant, antidiabetic, antifungal, drug delivery, drug carrier, wound healing, bioimaging, gene delivery, biosensors, and many more. The also have various advantages and disadvantages. The FDA has ZnO NPs on its list of safe substances. Zinc oxide nanoparticle is among one of the most researched studies conducted due to its ability to apply in varied downstream applications. Zinc oxide nanoparticles are a potential new generation of agent for a variety of medical conditions.

KEYWORDS: Zinc oxide (ZnO), Anti-cancer, Sol-gel, Biosensors, Nanowires, Bioimaging.

INTRODUCTION

In several fields, including physics, chemistry, electronics, optics, materials science, and the biological sciences, nanomaterials have numerous uses and consequences [1]. The potential antibacterial properties of Ag, Au, ZnO, TiO2, CuO, and Fe2O3 nanoparticles of metals and metal oxides are now gaining attention. ZnO is used extensively in both engineering and medicine. ZnO nanoparticles are utilized in engineering for a variety of applications, including solar cells, and gas sensors, particularly those for liquefied petroleum gas (LPG) and EtOH, chemical sensors, biosensors, LEDs, and photodetectors [2]. The metal oxide nanoparticles which are known as the most important are Zinc oxide nanoparticles (ZnO NPs). Due to their particular physical and chemical properties, they are used in several fields [3]. The direct band gap of Zinc oxide (ZnO) is (3.37eV) with an excitation binding energy of 60meV. These properties of ZnO make it a very unique material. It is of great use in near-UV emission, gas sensors, transparent conductors, and piezoelectric applications [4]. The chemical stability, high electrochemical coupling coefficient, a broad range of radiation absorption, and high photostability, are very unique physical and chemical properties of Zinc oxide. That's why it is also called a multifunctional material. These properties are responsible for the nanoparticle's unique and vast application in the biological and medical fields [6]. It is established that the management of physical and chemical features such as size, size dispersity, shape, surface state, crystal structure, organization onto a support, and dispensability is necessary for the diverse uses of ZnO nanoparticles [5]. ZnO nanoparticles are presently used in a variety of fields, including tissue engineering, cancer therapy, biosensing, drug and gene delivery, nanomachines that may mimic biological processes, and shape-memory polymers used in molecular switches, among others. A wide range of ZnO nanostructures, including nanoparticles, nanowires, nanorods, nanotubes, nanobelts, and other complex morphologies, have been created as a result of the widespread use of ZnO nanoparticles [6].

In the pharma industry ZnO nanoparticles have various applications and biomedical applications like antibacterial, antimicrobial, antifungal, anti-inflammatory, antidiabetic, antiproliferative activities, anticancer effects, treatment of different skin diseases, drug carrier and bioimaging.

CRYSTAL STRUCTURE OF ZnO

At ambient temperatures, the crystal structure of crystalline ZnO is wurtzite (B4). The ZnO wurtzite structure belongs to the space group C4 6V or P63mc and features a hexagonal unit cell with two lattice parameters, a and c. The structure is made up of two interpenetrating hexagonally closed-packed (hcp) sublattices, each of which is made up of a single kind of atom (Zn or O) that is displaced from the other along the threefold c-axis. It may be easily described graphically as a collection of alternate planes made of tetrahedrally coupled Zn2+ and O2 that are layered layer by layer along the c-axis direction. The non-centrosymmetric structure results from the coordination of ZnO in a tetrahedral form. Each anion is surrounded by four cations at the corners of the tetrahedron in wurtzite hexagonal ZnO, demonstrating tetrahedral coordination and exhibiting sp3 covalent bonding [7].

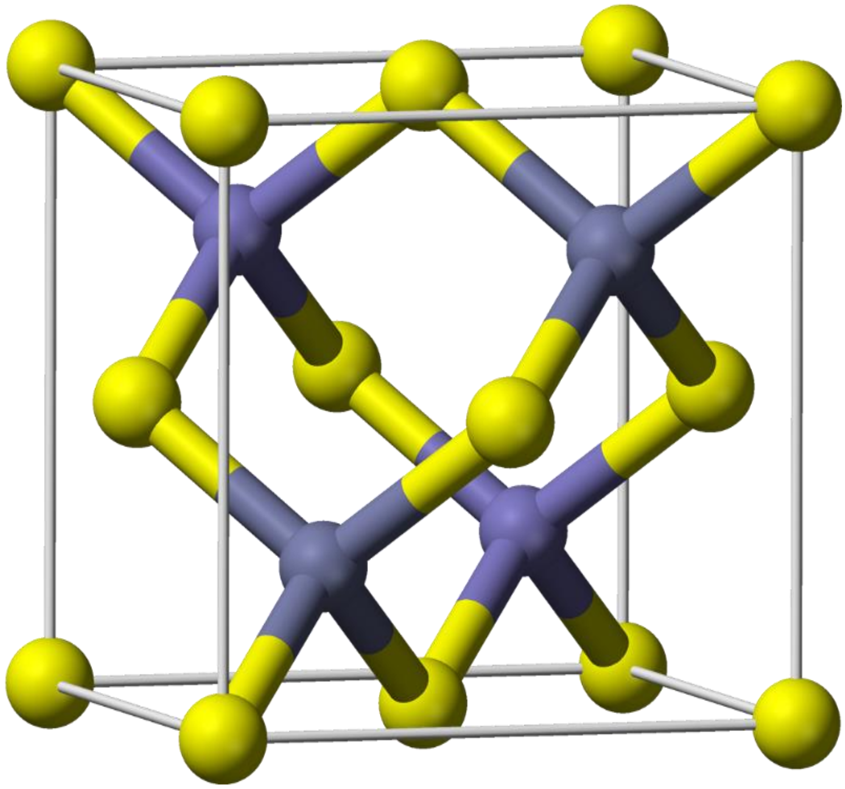

Fig 1. Structure of ZnO

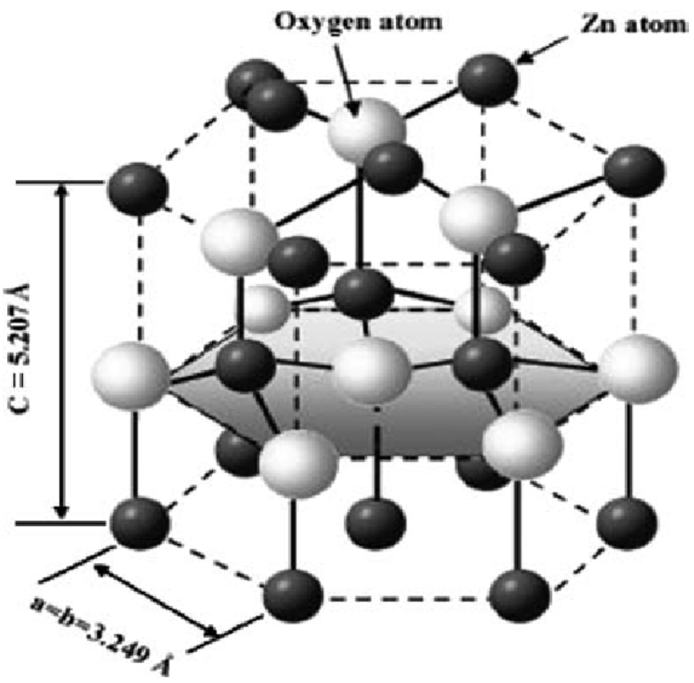

Fig 2. Wurtzite structure of ZnO

ZnO NANOPARTICLES

Numerous synthetic techniques have been used to generate a range of ZnO nanostructures, including nanoparticles, nanowires, nanorods, nanotubes, nanobelts, and other complex morphologies, due to its wide range of applications [8]. Laser ablation, hydrothermal processes, electrochemical depositions, sol-gel chemical vapour deposition, thermal decomposition, combustion processes, ultrasound, microwave-assisted combustion method, two-step mechanochemical-thermal synthesis, anodization, co-precipitation, electrophoretic deposition, and precipitation using solution concentration, pH, and washing medium are some potential methods for producing ZnO nanoparticles. At normal temperature, ZnO has a large band-gap with an energy gap of 3.37 eV [9].

ZnO nanoparticles are ZnO particles that are fewer than 100 nm in size. They can be made in a variety of ways, including solid, liquid (i.e., chemical), and gaseous forms. Chemical techniques come in many forms, including the mechanochemical process, precipitation process, precipitation in the presence of surfactant, sol-gel method, solvo-thermal method, hydrothermal method, emulsion method, and micro-emulsion method [6]. The primary importance of nanoparticles is that by shrinking to the nanoscale, they may generate new, distinctive physicochemical, structural, electrical, and magnetic characteristics that are absent from their larger or bulkier forms [10]. The exploration of ZnO's usage as a novel antibacterial agent has been prompted by the manufacture of nanoscale ZnO. ZnO-NPs have exceptional antibacterial and antifungal qualities in addition to having strong catalytic and high photochemical activity. ZnO has a strong optical absorption in the UVA (315–400 nm) and UVB (280–315 nm) areas, which is advantageous in the antibacterial response and utilised as a UV protector in cosmetics [11].

Fig. 3 ZnO Nanoparticles

Mechanism of action of ZnO NPs [12]

A typical wide band-gap semiconductor is ZnO. Its special characteristics make it suitable for a range of biomedical purposes, including anticancer, antibacterial, and antifungal ones. The majority of ZnO NPs' uses in biomedicine are related to their capability to produce ROS, which can cause cell death if the antioxidative capacity of the cell is exceeded. Their capacity to produce ROS is influenced by ZnO's semiconductor characteristics. The band gap, a void region stretching from the top of the filled valence band to the bottom of the unoccupied conduction band, measures around 3.3 eV for crystalline ZnO. The electrons in semiconductors have energies inside certain bands. UV radiation has enough energy to move electrons into the conduction band, leaving holes (h+) behind. h+ and electrons move to the surface of the NPs and react with oxygen and hydroxyl ions, respectively. This leads to the formation of superoxide and hydroxyl radicals. Due to the crystal flaws of nanoscale materials, ZnO NPs contain many valence-band h+ and/or conduction-band electrons even when UV light is not present. The numerous ROS generated subsequently set off redox-cycling cascades in the cells, resulting in oxidative damage that is irreversible. Other pathways for ZnO NPs' biological activities include necrosis and apoptosis. ROS-induced DNA damage triggers the release of apoptogenic substances from the mitochondrial intermembrane space, which in turn triggers apoptotic pathways. As a result, apoptosomes are created, and when executioner enzymes are activated and their particular substrates are cleaved, apoptosis and cell death result. Another mechanism is that following absorption, ZnO causes apoptosis in macrophages by rapidly dissolving inside their acidic lysosomes of the macrophages after uptake of ZnO in particulate agglomerated form.

SYNTHESIS OF ZnO NANOPARTICLES

There are various methods for the synthesis of ZnO nanoparticles:

1. **Hydrothermal Method**
   Stock solutions of Zn(CH3COO)2.2H2O (0.1 M) were produced in 50 ml of methanol while being stirred in order to generate the ZnO nanoparticles. To this stock solution, 25 ml of a methanol-prepared NaOH solution (ranging in concentration from 0.2 M to 0.5 M) was added while stirring continuously in order to bring the reactants' pH values to between 8 and 11. These solutions were put into teflon-lined, vacuum-sealed stainless-steel autoclaves and kept there for 6 or 12 hours at varied temperatures between 100 and 200 degrees Celsius. After then, it was allowed to naturally cool to room temperature. The finished white solid products of the reaction were filtered, washed with methanol, and then dried in air in a laboratory oven at 60o C [13].
2. **Precipitation Method**
   Zinc nitrate and KOH were used as precursors in the direct precipitation approach to create ZnO nanoparticles. In this study, deionized water was used to create the aqueous solutions of zinc nitrate (Zn(NO3) 2.6H2 O) and potassium hydroxide (KOH), respectively. A white suspension was created after adding the KOH solution slowly while vigorously swirling it into the zinc nitrate solution at room temperature. The white product underwent a centrifugation process at 5000 rpm for 20 min, three washes with distilled water, and a final wash with pure alcohol. The final product was calcined for three hours at 500°C in an air atmosphere [14].
3. **Sol-gel method**
   Numerous studies have been conducted on the sol-gel approach for producing metal oxide nanoparticles. A "sol" suspension is created for the sol-gel technique, which is

then used to create viscous gels and solid materials by processes including hydrolysation, condensation, and polymerization. The size of ZnO nanoparticles may be influenced by a number of variables, including the type of the alkyl group, the concentration of each precursor, temperature, the water-to-alkoxide molar ratio, and the presence of acid or basic catalysts. Faster nucleation, growth, and excellent purity of the resulting nanoparticles are the key benefits of the sol-gel process. The method's drawback is the expensive price of the precursors. When making ZnO nanoparticles, two researchers looked at the structure of the zinc acetate-derived precursor in sol-gel method. The outcomes demonstrated that once Zn(Ac)2 was dissolved in ethanol, Zn4O(Ac)6 had already begun to develop. One important element in the synthesis of monodispersed ZnO nanoparticles was the reflux period. the creation of ZnO nanoparticles utilising zinc acetate and potassium hydroxide as precursors, followed by their stabilisation and purification. The outcomes demonstrated that stabilised ZnO nanoparticles may be totally redispersed in methanol. Dejene recently used the sol-gel technique to create ZnO nanoparticles by adjusting the molar ratio of zinc acetate to sodium hydroxide. It was shown that the molar ratio of the precursors had an impact on the structural characteristics and particle sizes of ZnO nanoparticles. Controlling the properties of ZnO nanoparticles requires choosing a suitable molar ratio of the precursors.

4. **Mechano-chemical Method**

ZnS, CdS, ZnO, SiO2, and CeO2 are just a few of the numerous types of nanoparticles that have been synthesised using the mechano-chemical approach. In this method, zinc salts like ZnCl2, Zn(NO3)2, and ZnSO4 as well as carbonate salts like Na2CO3 and (NH4)2CO3 are often processed concurrently to create zinc carbonate (ZnCO3) through a chemical exchange reaction. Localized heat and pressure at the contact surfaces cause the reaction. After that, calcination can be used to produce ZnO nanoparticles. Due to its ease of use and low cost, the mechano-chemical approach is appropriate for producing ZnO nanoparticles on a large scale. Additionally, there are no organic solvents used in this procedure. The method's aggregation of particles during milling is one drawback [16].

5. **Other Methods**

- Wet chemical analysis
- Solid state pyrolytic method
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BIOMEDICAL APPLICATIONS OF ZnO NANOPARTICLES

ZnO NPs have been extensively researched for use in a variety of medicinal applications, including medication delivery for the treatment of cancer, diabetes, infection, and inflammation (Fig. 4)

Fig.4 Biomedical Applications of ZnO Nanoparticles

1. **Anticancer Activity.** [17]

   Chemotherapy, radiation, and surgery have become the standard treatments for cancer, a disorder marked by unchecked malignant cell development. Although all of these treatments appear to be quite successful in eliminating cancer cells in principle, they also come with a number of harmful side effects. Recent research has shown that nanomaterial-based nanomedicine has the potential to overcome these adverse effects due to its high biocompatibility, ease of surface functionalization, ability to target malignancy, and drug transport capability. Adults require Zn^{2+} as a nutrient, and ZnO nanoparticles are thought to be harmless in vivo. ZnO NPs can be chosen as biocompatible and biodegradable nanoplatforms based on these benefits, and they can also be investigated for use in the treatment of cancer. Various methods are given below:

   - Anticancer Activity by Inducing Cancer Cell Apoptosis
   - Anticancer by Autophagy.
   - Anticancer Drug Delivery.
   - Targeting Functionalization

2. **Antibacterial Activity of ZnO-NPs [18]**

   Pharmaceutical medication agents can be divided into organic and inorganic components. Organic pharmaceutical compounds are shown to be less stable than inorganic pharmaceutical agents at high temperatures and pressures. When used in the formation of microscale and nanoscale systems for therapeutic purposes, ZnO-NPs has proved to be a potent medicinal pharmacological agent. Although ZnO-NPs appear to have more medicinal drug activity than its microparticle counterparts, the specific processes by which medicinal drugs function are yet unknown. The ZnO-NPs show germicidal effects on both gram-positive and gram-negative bacteria, and they also have drug-like efficacy against high-temperature and high-pressure resistant spores. The literature makes it clear that the extent and concentration of ZnO-NPs' medical pharmacological action are important factors, whereas the influence of their crystalline structure and particle shape is negligible. Therefore, the more nanoparticles there are and how much more there are of them, the more potent the medicine will be. ZnO-NPs' medical medication activity's mechanism is yet not fully known. While it is also noted that the adsorption of particles on the bacterial surface owing to static forces might be another element, some researchers have claimed in their study that the creation of hydrogen peroxide is the key issue of medicinal drug action. Results showed that ZnO-NPs had antibacterial activity that seemed to be higher than that of microparticles. With increased particle dose, treatment period, and production process, the efficacy of nanoparticles will rise. Furthermore, it is undeniably undeniable that the surface area to volume ratio and particle size variation of green ZnO-NPs are the primary contributors to the significant increase in antibacterial activity seen in these information results. It is advised that inexperienced ZnO-NPs be employed since they have the potential to be useful in applications including food safety, agriculture, and future medical problems.

3. **Bioimaging** [19]

ZnO's broad band-gap semiconductor qualities can be used to kill cells by generating ROS, but its built-in photoluminescence capabilities may be used for biosensing applications. Wang et al. created ZnO-gated nanoplatforms for guided pH-triggered on-demand drug release and multimodality bioimaging. In vitro and in vivo trimodal imaging using ZnO NPs as contrast agents have also been used to provide thorough information for tumor diagnosis. When model leukemia K562 cells were treated with ZnO nanosheets, yellow-orange light emission was clearly seen around or inside the cells under UV excitation, indicating that these ZnO nanostructures had successfully penetrated the cells. Intradermal and intravenous injections of photoluminescent ZnO@polymer core-shell NPs were employed by researchers for mouse imaging. Using ZnO nanowires for molecularly targeted imaging of cancer cells after functionalization to make them water soluble, biocompatible, and less toxic, Hong and coworkers also investigated the imaging capabilities of ZnO. RGD peptide-conjugated green fluorescent ZnO nanowires were used to optically image integrin avb3 on U87MG human glioma cells. These findings offer up new directions for study into the application of ZnO-based compounds in bioimaging and therapeutic monitoring.

4. **ANTIFUNGAL ACTIVITY [20]**

In addition, Botrytis cinerea and Penicillium expansum were resistant to the antifungal effects of zinc oxide nanoparticles. Four different concentrations of zinc oxide nanoparticles (7015 nm) were used: 0, 3, 6, and 12 mmolL^{-} 1. Zinc oxide nanoparticles induced fungal hyphae to distort and alter in cellular makeup, according to SEM. B. cinerea and P. expansum's growth was suppressed at concentrations more than 3 mmolL^{-} 1. Additionally, it prevented the development of P. expansum's conidiophores and conidia, ultimately killing the fungus' hyphae [67].

5. **Anti-Inflammatory activity [21]**

   Given ZnO's well-known anti-inflammatory properties, Ilves et al. evaluated the effectiveness of bulk and nano-ZnO and discovered that only nano-ZnO could reach the deep layers of allergic skin. Additionally, local skin inflammation might be better controlled and systemic IgE antibody production could be promoted by nano-ZnO. According to the authors, the ability of B cells to produce IgE is affected by non-specific reactions brought on by released Zn2+.

6. **GENE DELIVERY [22]**

   Surface-coated nanoparticles are essential for the transport of genes. In a research, positive poly (2-(dimethylamino) ethyl methacrylate) (PDMAEMA) polymers coated on zinc oxide QDs condense p DNA for use in gene delivery. According to a different study, 3D tetrapod-shaped zinc oxide nanoparticles work as gene vectors to transport pEGFPN1 DNA to human melanoma cells (A375).

7. **Antidiabetic activity [23]**

   Based on the discovery that zinc plays a significant role in the production, storage, and secretion of insulin, researchers have investigated the antidiabetic effect of ZnO NPs. In a recent study, diabetic rats were used to examine ZnO nanoparticles' antidiabetic effect and compare it to ZnSO4's. Compared to ZnSO4, ZnO NPs were discovered to have stronger antidiabetic efficacy, which was demonstrated by better insulin sensitivity, glucose disposal, and zinc status. Wahba discovered that ZnO NPs successfully repaired diabetes-related pancreatic damage as evidenced by improvements in structural and ultrastructural quality as well as biochemical normalisation of blood sugar and serum insulin. To increase the effectiveness of the anti-diabetic medications red sandalwood and vildagliptin, ZnO NPs have also been studied in conjunction with them.

8. **Antimicrobial Potential of ZnO-NPs**

   In both microscale and nanoscale formulations, ZnO is being studied as a possible medication agent. Although the precise mechanisms of medication action are not fully understood, results have shown that ZnO-NPs exhibit medication activity that is reportedly greater than that of small particles. It has also been suggested that the majority of the causes of cell swelling are the rule of ROS that generate on the surface of particles, zinc ion release, membrane dysfunction, and nanoparticles acquisition area unit [24]. Treatment of ZnO-NPs at high temperatures has a significant influence on their medicinal action, whereas treatment at lower temperatures results in less activity. The mechanisms of medicament activity of ZnO-NPs aren't well understood and although it is projected that the generation of oxide can be the main issue of this activity, yet it is indicated that the binding of the particles on microorganism surface, owing to the electricity forces, can be a mechanism study regarding the medicament behavior of ZnO-NPs which can be done by employing a chemiluminescence and oxygen electrode analysis [25]. Metal nanoparticles area unit are extremely ionic and may be ready with extraordinarily high surface areas, along with uncommon crystal and morphologies that possess varied edge/corner and different reactive surface sites. ZnO-NPs area unit is being studied in unison with medical procedure ablation regimens [26]. Although it is predicted that the production of oxide may be the primary factor influencing this activity, it is also suggested that the binding of the particles to the surfaces of microorganisms as a result of electrical forces may be a mechanism study regarding the medicament behaviour of ZnO-NPs. This can be accomplished by using chemiluminescence and oxygen electrode analysis [25]. Exceptionally ionic metal nanoparticles may be produced with extremely large surface areas, unusual crystal structure morphologies with varying edges and corners, and a variety of reactive surface sites. ZnO-NPs are being explored in conjunction with ablation therapy regimens for medical procedures [26]. Nanoparticles will give antineoplastic medical speciality that shows a synergistic antineoplastic effect in the presence of warmth in addition to having a stronger thermal impact on neoplasm ablation. They may even be scanned to achieve accuracy in medical assistance. According to some studies, it would be possible to create nanoparticles with the right composition and characteristics to enhance the ablation property by using the molecular process involved in the ablation of tumor-mediated nanoparticles [27].

9. **GENE DELIVERY**

When nanoparticles are surface coated, they play a vital role in gene delivery. In a study, zinc oxide QDs, when coated with positive poly (2-(dimethylamino) ethyl methacrylate) (PDMAEMA) polymers, condense p DNA for application in gene delivery. Another study reveals that zinc oxide nanoparticles that are 3D tetrapods act as gene vectors, which deliver pEGFPN1 DNA to human melanoma cells (A375) [28].

10. **BIOSENSORS** [29]

Biosensors are widely employed in biological studies and the food business and may be divided into several categories based on the way they detect things (photometric, electrochemical, etc.). Different kinds of biosensors employ zinc oxide nanoparticles:

- Glucose biosensors
- Phenol biosensors
- Cholesterol biosensors
- Lactic acid biosensors
- Uric acid biosensors
- Urea biosensors
- Hydrogen peroxide (H2O2 biosensors)
- Protein biosensors
- DNA biosensors

11. **Wound healing**

Due to its potent antibacterial qualities and the zinc's ability to stimulate the growth of new tissue, ZnO NPs have also been utilised effectively in wound dressings [12]. Recently, ZnO NP-loaded sodium alginate-gum acacia hydrogels (SAGA-ZnONPs) were created and demonstrated to have healing properties in sheep fibroblast cells at low ZnONP concentrations. ZnONPs were hazardous to cells at high concentrations, whereas SAGA-ZnONPs hydrogels greatly decreased the toxicity while maintaining the positive antibacterial and therapeutic properties [30]. Sprague-Dawley rats used in in vivo tests showed improved wound healing, quicker re-epithelialization, and increased collagen deposition [31].

12. **Cosmetic Application of ZnO Nanoparticles [32]**

ZnO nanoparticles have outstanding UV-blocking capabilities in addition to the aforementioned uses, such as gas sensors, chemical and biosensors, light emitting diodes, photo-detectors, and photocatalytic use. Sunlight typically emits three different forms of UV radiation: UV-A (320-400 nm), UV-B (290-320 nm), and UV-C. (250–290 nm). Since UV-A radiation makes up around 95% of all sunshine radiation, it is the major cause for worry. UV-B radiation makes up less than 5% of the total, whereas UV-C radiation has little impact since it is absorbed by ozone on Earth's surface [88-89]. Furthermore, UV-A radiation is regarded as being more harmful than UV-B radiation since it is 100 times more intense and may penetrate farther into the skin's dermis. Given the UV radiation levels given above, it is crucial to block these hazardous radiation types since prolonged exposure to them might result in skin cancer in people. Materials with UV-blocking capabilities are typically included to cosmetic formulas to protect the skin. In comparison to TiO2, ZnO nanoparticles offered an efficient UV-blocking substance for skin protection from UV-A radiation. TiO2 typically scatters UV-A wavelengths, but ZnO nanoparticles efficiently absorb rather than scatter this light. Although ZnO has better UV-A radiation absorption than TiO2 does, photocatalytic activity prevents ZnO from being used in cosmetic compositions. Additionally, because of ZnO's strong photocatalytic activity, reactive oxygen species are produced, which have the potential to oxidise components used in cosmetic formulations.

Advantages and disadvantages of different ZnO nanostructures [33]:

1. **Nanoparticles**

Advantage:

- Can be easily suspended in a solution
- Outstanding performance owing to their large surface areas

Disadvantage:

- Easily form agglomerates in solution, which contributes to reduced effective surface area
- Post-treatment for catalyst removal is required
- Complete recovery of catalyst is difficult

2. **Nanowires**

Advantage:

- Growth could be easily carried out on most substrates
- Lower surface area compared to nanoparticles
- Post-treatment to remove catalyst is not required
- Lower crystallinity and more defects

Disadvantage:

- Growth conditions are highly restricted Consists of large effective surface area compared to nano-thin films

3. **Nano-thin film**

Advantage:

- Can be coated on certain substrates

Disadvantage:

- Performance is restricted by small surface area
- Post-treatment to remove catalyst is not required

CONCLUSION

This analysis primarily focuses on nanoparticles, whose special features are demonstrating their growing utility in several industries. Based on their anticancer, antibacterial, antidiabetic, anti-inflammatory, drug delivery, and bioimaging properties, ZnO NPs have demonstrated promising biological uses. The FDA has ZnO NPs on its list of safe substances. When used as drug carriers to improve the efficacy of therapy, ZnO NPs are also well recognized for increasing the bioavailability of medicinal medicines or biomolecules. Overall, compared to traditional chemical antimicrobial treatments, metal oxide ion-based nanomaterials display broad-spectrum biocidal action against a variety of bacteria, fungi, and viruses. Zinc oxide nanoparticles are a potential new generation of agent for a variety of medical conditions.

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