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Review article

Modern perspectives on biomedical applications of ZnO nanomaterials

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ABSTRACT

With extraordinary success, the past few decades witnessed high growth in nanoscience or nanotechnology that is turning towards innumerable dynamic sectors providing new pure as well as applied opportunities such as physics, chemistry, material, biology, medicine and many more. Day by day the advancements in the field of nanotechnology have been explored due to the high surface area, and multifunctional with acceptable biocompatibility make them capable to play the countless role of highly multifunctional-tailored drugs delivery alternates, phototherapy, bioimaging and gene delivery to develop new nanomaterials with various possible applicabilities. Numerous researchers have conducted various studies on the applicability of ZnO nanomaterials in the area of environment, biomedical and healthcare sectors Here, recent progress and modern perspectives are presented concerning ZnO nanomaterials for their biomedical applications.

Keywords: Nanoscience, Nanomaterials, ZnO, Drug delivery, Tissue engineering, Nanomedicine, Sensor, Diabetes.

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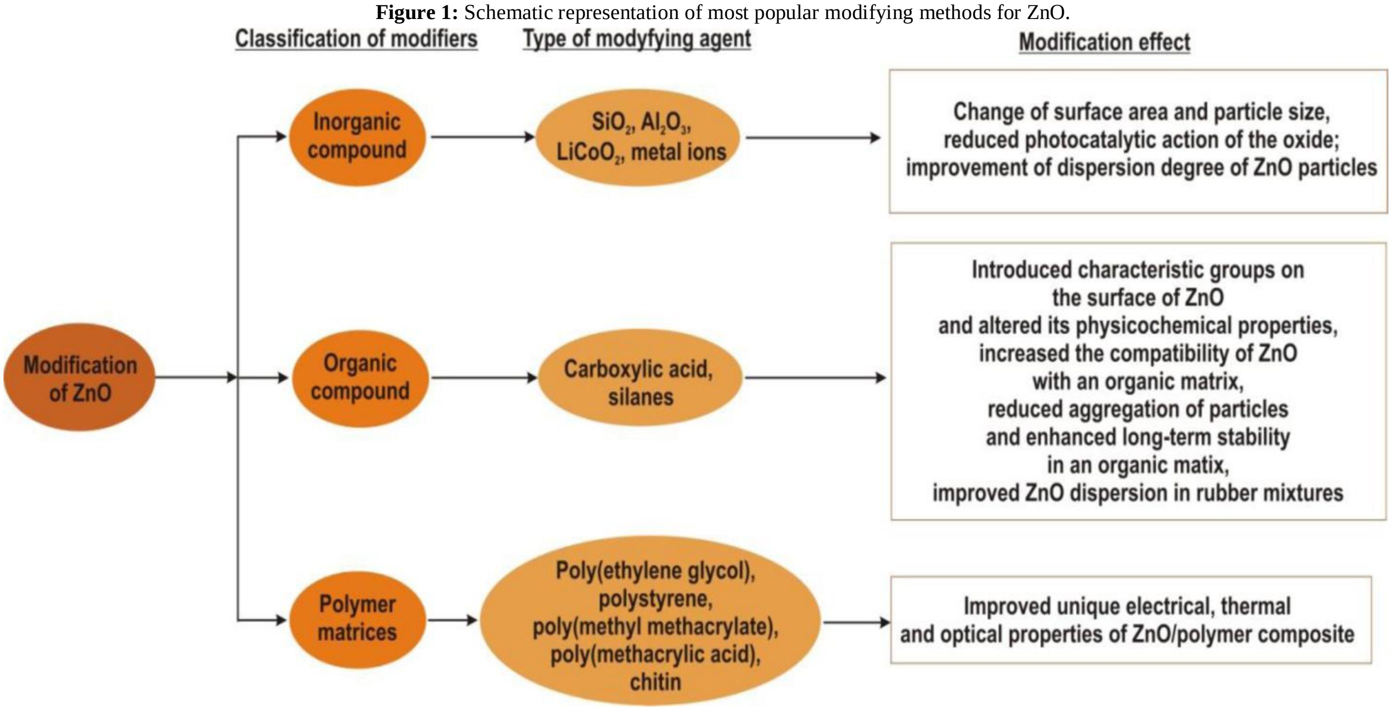
INTRODUCTION

In the 21st century, nanotechnology is emerging as an advanced science with materials having multipurpose and multiple applications. The past few decades witnessed promising breakthroughs in nanomaterials wide applicability in diversified sectors such as materials and manufacturing, agriculture, biomedical, bio-electronics, bio-engineering, healthcare, energy etc. due to their high ratio of surface area to volume, easy functionalization on surface and their multimodal conjugation possibility with different functional groups [1]. As an upshot opportunity through the extended use of different nanomaterials has revolutionized them for their applications in the biomedical field significantly [2]. The different properties like better functionality, biodegradation capability and biocompatibility of nanomaterials make them a reliable and vibrant alternative to their conventional ones. In this review, we highlight the current and future scope of ZnO nanomaterials in various applications of biomedical.

The cuboid zinc blende ZnO structure is found stable with a large bandgap (3.37 eV) and large exciton binding energy (60 MeV) at ambient temperature [2,3], making ZnO an important material, particularly in the area of semiconductors applications. Zinc ore on heating in a shaft furnace provides metallic zinc in a vapour form, gases passed away through conduit and condensate is achieved as zinc-oxide for several applications [4-6]. ZnO is an ingredient of different medicines, cosmetics and food additives and is consumed by us in daily life for a very long time. Historical and modern evidence both provide information that ZnO has low toxicity and is biodegradable material [7], which proved its potential in applications in biomedical sciences [4,8]. A Persian physician and philosopher, Avicenna has written about ZnO in his book, *The Canon of Medicine, as a preferred cure for multiple skin diseases, including skin cancer* [9]. The modification of ZnO materials can be achieved through three main modifiers such as inorganics, simple organics and polymeric adductions (Figure 1). The semiconductor properties of ZnO make it good for a number of photo-induced applications including photo-catalyses and photoemission [10]. Electron–hole pairs are generated in the conduction and valence bands by absorption of ultra-violet light of a wavelength of short than 400 nm by ZnO. The electrons orbital band also called as conduction band contains excited electrons (e−) jumped from the valence band. The valence band is the outermost electron orbital of an atom of any material. The difference between the highest occupied energy state and the lowest unoccupied energy state is such that the valance band and conduction band are called a bandgap. Electrons (e−) are excited to jump into the conduction band, leaving holes (H^+) in the valence band. Electrons and holes both can participate in the physiological activities of the cells. They can generate ROS by reacting with oxygen or water, which are superoxide and hydroxyl radicals [11]. In an inverse process, photons are emitted by recombination of electron-hole pairs, which allows the application of ZnO for bio-imaging [12]. ZnO is structured as crystal *e.g.* zinc blende, rock salt and wurtzite, hexagonal wurtzite is found thermally most stable among these [13]. ZnO NPs acid-sensitive polymers conjugated chemically taken up by cancer cells through endocytosis, and preloaded anti-cancer drug dependent on pH is released into cellular lysosomes [14].

Figure 1: Schematic representation of most popular modifying methods for ZnO.



ZnO nanostructures not only gained their importance in chemical drugs but also in protein antigens. The ZnO nanostructures and plasmid DNA can be delivered and expressed in eukaryotic cells [15-17]. In another recent work, MgO nanoparticles are incubated and fabricated inside the ZnO NPs, to form MgO /ZnO nanocomposite for biomedical applications. Rai et al, 2021 prepared the particle size as 56 nm, 400 nm, and 450 nm, respectively for MgO, ZnO, and MgO/ZnO nanopowders and secondary electron images are observed in field emission electron microscopy [18,19]. Herein we have described the modern biomedical perspectives of ZnO nanomaterials in view of plenty of literatures.

Biomedical Applications

The requirement of ZnO in a wide range of applications, demands a low-cost, highly stable and reproducible synthesis which can make it a safe alternative [20,21]. Green syntheses techniques can produce important and diversified morphologies. ZnO NMs are ever-present in many biological applications and their toxicological effects are assessed [22]. In a very recent work consideration is given to antibiotic agents based upon ZnO NPs/MPs as antibiotic alternatives and aids for clinical and industrial applications [22]. In this study, ZnO-NPs are found highly successful cytotoxic for cancerous in vitro against Caco-2 (IC50 = 9.95 ppm) as compared with normal (WI38) cell line (IC50 = 53.34 ppm) [23]. Several biomedical applications are described as under

Bioactive surfaces

Today, multifunctional textiles have been used to impart antibacterial, UV protection functionalities as the essential part of the field of healthcare functionality by the use of biologically active macromolecules produced from fungi, flora and fauna and nanomaterials [24-26]. Indeed, biologically active molecules open the scope of green technology and can explore novel applications based on nanotechnology. In children's treatment cases, Epidiolex (purified cannabidiol) is approved by regulatory, drug-resistant epilepsy have set a yardstick and prescribed cannabinoids [27]. Recently, new weapons that have been constantly taken under consideration in combating cancer were prepared by several research groups around the globe based on the functional nanomaterials in conjugates and biopolymer assemblies [28-32].

Enzyme Activity

A study on treatment on rats for 10 days was done for activities of the enzyme under the action of ZnO NPs oleogels at the dose of 25 mg·cm−2 per day. Data under the action of ZnO NPs oleogels is presented in tabular form showing a decrease in malonic dialdehyde (MDA) level and plasma as in erythrocytes. There are interesting and unexpected facts that normally ZnO NPs become the cause of the generation of reactive oxygen species [33,34].

It was investigated the effects on bacterial community and soil enzyme activity by copper hydroxide nano fertilizer formulation

(NFF) are investigated for single-time and multiple-time applications. 21 days of observation of Cu in soil (48 mg (Cu)/kg: the recommended dose of NFF) for one or three applications are taken. In addition to this dispersing agent of NFF, ionic fertilizer and active ingredients were also tested [35]. Progress of applications of ZnO NPs in biomedicine revealed that less than 100 nm-sized ZnO NPs are more biocompatible and help in different biomedical research and applications.

Drug Delivery

Tumour-triggered targeting technique for drug delivery is used to fabricate dual-pH-sensitive chitosan (CHI)/mesoporous silica nanoparticle (MSN) [36]. Using Nanoparticles is much safer and more effective for cancer treatment in a targeted drug delivery system. Specific sites of cancer cells targeted by nanoparticle-based drug delivery systems help to reduce the number of drugs used and hence minimize the side effects [37,38]. Drugs loading on ZnO NPs good at biodegradability, solubility and toxicity, and can be delivered in a better way into the cancer cells as compared to individual agents e.g. curcumin, doxorubicin, paclitaxel, and baicalin or DNA fragments loaded on ZnO NPs [39-41]. Recently, Fe3O4-ZnO core-shell nanoparticles with an average diameter of 16 nm which can serve as imaging contrast agents were prepared to deliver carcinoembryonic antigen into DCs [16].

By using the co-precipitation technique Hariharan et al. prepared PEG 600 solution-modified ZnO nanoparticles (ZnO/PEG NPs), to make DOX-ZnO/PEG nano-composites by loading doxorubicin [40]. DOX-ZnO/PEG nanocomposites present dependence on the concentration of inhibition on cervical cancer HeLa cell proliferation and enhance the intracellular accumulation of DOX. ZnO nanorods are prepared by Deng and Zhang using chemical techniques and are used to carry DOX in the manufacturing of a DOX-ZnO nanocomplex [41]. In the case of SMMC-7721 hepatocarcinoma cells, DOX-ZnO nanocomplexes import DOX into SMMC-7721 cells increasing the cellular uptake capability of DOX. DOX-ZnO nanocomplexes result in more cell death rate when coupled with ultraviolet radiations, through photocatalytic properties and synergistically triggered caspase-dependent apoptosis.

Synthesis of pH-sensitive, hollow ZnO-nanocarriers loaded with paclitaxel is done and its effectiveness *in vivo* and *in vitro* is studied for breast cancer [32-26]. Soy lecithin liposomes (SLP) were prepared and modified the surface partially with methoxy polyethylene glycol-cholesterol conjugate (mPEG-Chol) to get an improvement in the efficiency of poor-solubility of water-anticancer-drugs delivery [8,30]. An increase in the drug concentration shows some regularity in drug loading contents and efficiency [30]. Dhivya et al. fabricated two co-polymer-encapsulated ZnO NPs for carrying curcumin, Cur/PMMA-AA/ZnO NPs nanocomposites and Cur/PMMA-PEG/ZnO NPs to get increases in bioavailability and solubility of curcumin [42]. In very recent work, the anticancer drug doxorubicin (DOX) was investigated through the interaction and bond properties of armchair single-walled carbon nanotubes (SWCNT) functionalized with hydroxy and carboxy substitution by DFT design [43].

Gene Delivery

Cancer treatment is influenced by gene therapy over the last several decades [9,26]. Developing safe gene vectors for protecting DNA from degradation and enabling cellular uptake of DNA with high efficiency is a major problem. A wide variety of nanomaterials including ZnO nanomaterials are under research for gene delivery and gene therapy applications [30-33]. ZnO nanostructures tetrapods are good gene vectors for the delivery of pEGFPN1 DNA to A375 human melanoma cells [37-38]. Plasmid DNA (pDNA) gets electrostatic interactions and is attached to ZnO nanostructures and the gene delivery is supported by three needle-shaped legs that support the internalization of tips in cells. In this cytotoxicity is not observed and is responsible for three-dimensional geometry. pDNA can be condensed well for gene delivery by coating ZnO QDs with positively charged poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) polymers [44]. Large pDNA such as a luciferase reporter gene are condensed by polymer-coated ZnO QDs with a quantum yield of >20%, ZnO QDs help in COS-7 cells and can be transfected with pDNA with low cytotoxicity. ZnO QDs are efficient in reducing cytotoxicity by polymethacrylate in the QDs, which are negatively charged and interact with the positive charges.

Diabetes Treatment

In 2014, the report published by WHO on diabetes mellitus indicated that there is a severe public health concern and approximately more than 400 million adults are found diabetic around the globe [6,16]. The incapacity of the body to produce insulin or the ineffective use of the insulin produced causes a metabolic disease named diabetes mellitus [22-24]. Natural extracts of red sandalwood (RSW) and ZnO NPs conjugation agent are found very effective in diabetes [2]. The was assessed with the help of an Inhibition assay of α-amylase and α-glucosidase with murine pancreatic and small intestinal extracts found supporting for testing antidiabetic activity [12]. Diabetes mellitus (DM) is a chronic disease that results in complications in the kidney, reproductive system, and liver systems. High blood glucose, insulin secretion deficiency or insulin resistance are some characteristics of Diabetes mellitus [36].

Hussein et al. reported that ZnO NPs composited with hydroxyl ethyl cellulose were found a considerable stabilizing mediator to relieving diabetic worries [45]. All over the world the change in lifestyle and other reasons are common metabolic disorders and result in diabetes mellitus. In diabetes mellitus, Abdel-Latif et al. 2021 find the role of glucose transporters (GLUT) and numerous therapeutic options are assumed that can control the plasma glucose levels [42-45].

Anti-inflammatory Activity

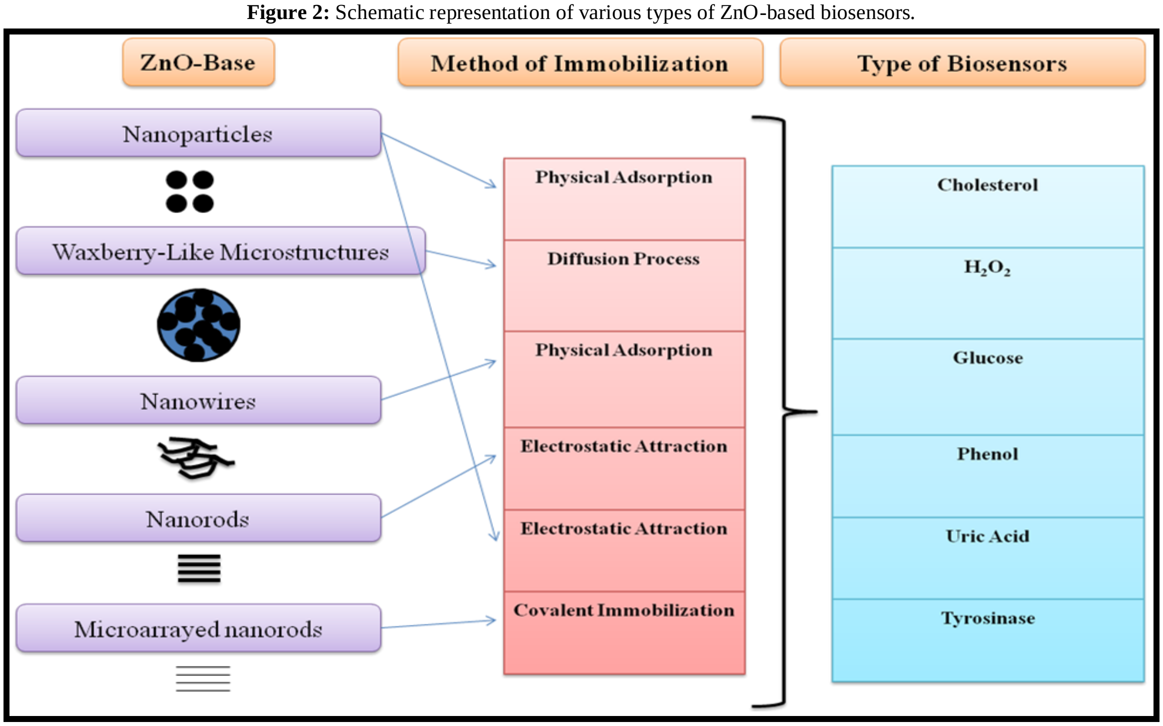
Anti-inflammatory activities and antioxidant assays are analyzed by spectrophotometer e.g. production of NO with the addition of bioactive components. Due to the biological activities of zinc ions, ZnO NPs have been found anti-inflammatory effects. Impairment of the skin-barrier functions results in a chronic inflammatory skin disease named atopic dermatitis (AD) and a complex mechanism of interaction of genetic and environmental factors is occurred [33,41]. Textiles remain in contact with human skin for the longest time and most intense contact. Wiegand explored in vitro and in vivo ZnO-functionalized textile fibers which can control the oxidative stress in AD and it can treat many inflammatory processes, like arthritis, rheumatism and its associated pain [46]. ZnO-based textiles are highly antioxidative and antibacterial in nature AD pruritus and subjective sleep quality are found to improve when ZnO-based textiles are worn by AD patients overnight for 3 consecutive days.

According to observations of Ilves et al., ZnO NPs of various sizes are capable to penetrate the injured and injured allergic skin in the AD model mouse [47]. Dose-dependent ZnO NPs are anti-inflammatory active suppressing the production rate of NO as well as the related protein expressions of iNOS, IL-1β, IL-6, COX-2 and TNF-α. Extracts of mangrove plants, *Heritiera formes* and *Sonneratia apetala* are used to prepare ZnO NPs by Thatoi et al. under photo-condition and with higher potential for anti-inflammation in ZnO NPs (79%) than the Ag nanoparticles (69.1%) [44,47].

Bio-Imaging

ZnO NPs have near-UV emissions radiations and blue emissions radiations, have luminescence of green or yellow related to oxygen vacancies and are found suitable for extending their applications into the bioimaging field [8,7]. For the very first time, stable aqueous ZnO@polymer core-shell nanoparticles were prepared using a sol-gel method by Xiong et al. (ZnO@poly(MAA-co-PEGMEMA) [44]. In aqueous solutions, ZnO@polymer core-shell nanoparticles, have been found with very stable with broad photoluminescence and exhibit great quantum yield. Less than 0.2 mg/mL of concentrated nanoparticles are not found in a markable toxicity hepatoma cell of humans. During the cell culture process, luminescence was found very stable and the cells lived for 45 min on exposure. So, ZnO@polymer core-shell nanoparticles can be used as fluorescent probes for cell imaging in vitro for cheap and safe luminescent labels [12,44]. This gets attached to the NIH/3T3 cells on the surface and different fluorescent colours are displayed with different radiations of wavelengths. Cell imaging, intrinsic fluorescence and pathological studies are some advantages of ZnO nanomaterials. Verma et al. (2021) reported variable optical properties and fluorescent behaviour of ZnO NMs and concluded that they can be a suitable alternative option in bio-imaging agents [22]. Another report presents the dependability of ZnO morphology and SHG intensity on Ce-dopant concentration in ZnO for bio-imaging and bio-sensing (Figure 2) [22,23].

Figure 2: Schematic representation of various types of ZnO-based biosensors.



Antibacterial Activity

ZnO NPs are highly active and have a large specific surface area with antibacterial properties to block pathogenic agents. ZnO antibacterial toxicity mechanisms depend upon inducing the capability to generate excess ROS such as hydrogen peroxide, hydroxyl radicals and superoxide anion production [20-25]. ZnO NPs accumulated in the outer membrane or cytoplasm of bacterial cells and the release of Zn^{2+} get triggered, which may disintegrate bacterial cell membrane, damage the membrane protein, genomic instability and finally death of bacterial cells [23,47]. Evaluation of the antibacterial activity of ZnO NPs is done on aureus Gram-negative *Escherichia coli* and Gram-positive Staphylococcus *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Bacillus subtilis*, *Vibrio cholerae* and *Enterococcus faecalis* [23,42-44]. The antibacterial activity potency (*E. coli* and *S. aureus*) of crystallite small-size ZnO NPs is detected by Ohira and Yamamoto and found strong in comparison to crystallite large-size ZnO NPs [48]. ZnO NPs of ~13 nm size is made and tested on *E. coli* and *S. aureus* and a very good response of complete inhibition capability is observed at concentrations of about 3.4 mm for the growth of *E. coli* but also prohibits the growth of S. aureus at very low concentrations (≥1 mM). According to ICP-AES measurement, *E. coli* is very sensitive to Zn^{2+} than *S. aureus*. *Cholera* is an Epidemic disease that affects populations in developing countries [49], caused by the intestinal infection of Gram-negative bacterium. ZnO NPs behaviour for *Vibrio cholerae* is detected [48]. Observations on the growth of El Tor (N16961) biotype of *V. cholerae* show that ZnO NPs are more effective to prohibit its growth and hence can inhibit ROS production. ZnO NPs employed as antibacterial agents, such as mouthwashes, ointments, and lotions and can prevent bacterial adhering, breeding and spreading by coating medical devices substances. Therefore, ZnO NPs are responding better against Gram-positive and Gram-negative bacteria by acting as antibacterial agent.

Biosensors

Nanoscience and nanotechnology-based nanomaterials are present in different areas and are investigated for large applications. Nanomaterials and their combinations with biologically active substances are capable of developing biosensors with high performance [46]. Better Biocompatibility, low toxicity, high surface area and high electron transfer capability are some great characteristics for application as biosensors [15,43]. For analyzing cholesterol, H_2O_2, glucose, phenol, urea etc small molecules, ZnO-based biosensors can be used. Numbers of biosensors are under invention for making devices for medical applications and also for observing biological parameters such as pulse rate, oxygen level, glucose, respirations, alarms for medicine, exercise, food, nutrition uptake, wake-up, sleep and many more. These multi-detection capability sensors are miniature together referred to as an electronic nose or e-nose. A new research report by Kumar et al. gave the view that the use of novel electronic devices is increasing at a very fast rate, which led to an era of artificial intelligence and automation [49].

Glucose Biosensors

GOx-based biosensors can diagnose diabetes and are also used in the food industry. The sensitivity of ZnO-based biosensors is observed high due to the strong affinity of GOx for glucose. Tetragonal pyramid-shaped porous ZnO nanostructures when fabricated on a glassy carbon electrode (GCE) make glucose biosensors based on GOx [50]. Some biosensors for glucose are based on GOx and found as ZnO nanorod/Au nanocrystal matrix, ZnO nanoclusters doped with Co, carbon-decorated ZnO NW array and ZnS NCs monolayer coated on vertically grown ZnO NW [51]. Glucose detection response of 2.22 μM is achieved by making multiwalled CNTs on the glassy carbon electrode (GCE) used to put out of action to the first layer of GOx and electrodeposited ZnO nanoparticles coated with a second layer of GOx [52].

Cholesterol Biosensors

Among all molecules in the human body, cholesterol has its value in human life. Several diseases such as arteriosclerosis, hypertension and myocardial infarction are diagnosed by indicator serum cholesterol level [49-50]. A number of biosensors are invented for measuring the concentration of cholesterol by immobilizing cholesterol oxidase onto various ZnO nanomaterials [53]. Thin films of ZnO nanoporous developed on the gold surface, flower crystallized ZnO structures [54], ZnO nanospheres deposited electrically and combine thoroughly with Pt onto a GCE, hybrid ZnO nanorods functionalized with gold/platinum and constructed on multiwalled CNT modified GCE, hexagonal ZnO nanorods grown on the silver wire, ZnO nanowalls manufactured chemically on aluminium wires are some present time biosensors.

Other Biomedical Studies

In new work, for Zn tolerance, the structure of microanatomy and nucleolar activity in the roots and leaves of grapevines is observed. The high value of leaf mitotic index (MI) is observed in the case of Zn-treated grapevines and hence tonic growth in leaves occurs. An increment in the thickness of roots is observed and a decrease in root MI, mean nucleolar area and number by a higher quantity of Zn [51]. In recent work, Toledano et al. reported the use of ML-NPs for teeth before the canal filling due to dentinal tubules occlusion and radicular dentin structure reinforcement in endodontic treatment [52]. It is observed after 6 months shows the lower crystallinity of radicular dentin treated with undoped-NPs compared to treated dentin with ML-NPs. Dentin treated without NPs is found scanty re-mineralization potential and degradation. The wound

healing mechanism in rats is separate from humans since re-epithelialization in humans is observed less than that observed in the treatment of rats [53]. The study of burn wound healing in rats shows the rate of wound healing without and with the effect of zinc and betulin derivatives on collagen formation in various processes and the model is found cheap as well as simple [2,47,50]. Consequently, it is found that the animal groups under oleogels treatment had no loss in appetite, satisfactory wool condition and no deviations in behaviour as compared to animals of the untreated group. The healing process in the untreated animal group was slow on 1st and 10th day for burn wounds but the area of the burn wound is observed to be reduced from the 1st day [52-54].

Recently, some emerging pharmaceutical compositions based on ZnO NPs formulations composited with natural products have been found suitable to have vasodilatation activities. A new wound-healing drug Episalvan, a drug form of oleogel, extracted from birch bark, in sunflower oil is employed for healing I-II-degree burns [54]. Reflected radiations from tissue are analyzed using the Doppler frequency shift technique. Doppler frequency shift is proportional to changes in the speed of blood flow of erythrocytes motion in the microcirculatory system. The medium flow of erythrocytes per unit of time is observed in tissue on the microcirculation index. MI value less than 1 perfusion unit denotes a deep wound. ZnO NPs–triterpenoid oleogels can improve the microcirculation index value by 20–35% in the near-wound zone in 10 days using. 10th day, the microcirculation value is achieved equal to that of intact animals, which is a skin regeneration condition. A decrease in the depth of the wound is found as the perfusion index increases. Hence it is confirmed that there is a relationship between an increase in blood flow and perfusion index, with a decrease in wound depth. A relationship of healing of wounds and antioxidant biochemical indexes are related closely by the influence of zinc oxide nanoparticles. Some plant triterpenoids such as derivatives of madecassic acid, asiatic acid, betulinic acid etc. are efficient to activate collagen synthesis which is necessary for effective wound healing [35-38].

CONCLUSION

Several technological innovations have witnessed the successful usage of nanomaterials, especially in the biomedical sector in the last few decades. With plenty of interesting physicochemical properties and potential for several biomedical applications, ZnO nanomaterials are very good nanoplatforms for biomedical applicability. ZnO nanomaterials have been investigated for many biological performances and found considerable results. However, the toxicity of nanomaterials is a big question and quite important is how to modify nanomaterials to achieve a toxicity level minimum and to the safe limit for the human body so that they may find applicability in biological systems as well. At present time, the maximum study of the toxicology of ZnO nanomaterials is carried out in an artificial environment. Based on the above discussions, we recommend more efforts are required for the studies of the toxicology of ZnO nanomaterials in living organisms to pave the way for biomedical applications for fascinating nanomaterials in near future. Research on ZnO nanomaterials will flourish in biomedical applications in the next few years due to the exciting biomedical applications of this vibrant material.

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Conflicts of interest

Authors declare that there is no any conflict of interest

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