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Original Article

A Review: Zinc Oxide Nanocomposites and its Applications

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ABSTRACT

Zinc oxide (ZnO) nanocomposites have emerged as multifunctional materials due to their unique optical, electrical, and physicochemical properties. The incorporation of ZnO nanoparticles into diverse matrices has significantly enhanced their applicability in biomedical, environmental, and industrial domains. This review presents a comprehensive overview of the synthesis strategies and characterization techniques for ZnO nanocomposites, highlighting sol-gel, hydrothermal, and green synthesis methods as effective and scalable approaches. The structural and morphological properties of these nanocomposites, investigated through techniques such as SEM, TEM, XRD, and FTIR, confirm their tunable features, enabling controlled functionalization for target-specific applications. Biomedical applications, especially antimicrobial, anticancer, and wound-healing functionalities, have shown promising results due to the enhanced reactive oxygen species (ROS) generation and cellular interaction of ZnO-based materials. In the environmental sector, ZnO nanocomposites have demonstrated efficacy in water purification, photocatalytic degradation of pollutants, and as sensors for detecting environmental toxins. Additionally, their integration into electronic and optoelectronic devices underscores their versatility. The review also touches upon the toxicity and biocompatibility issues, emphasizing the need for careful design and assessment for safe biomedical use. Future directions focus on optimizing synthesis protocols, enhancing biocompatibility, and expanding application horizons through interdisciplinary approaches. Overall, ZnO nanocomposites hold significant potential in advancing next-generation nanotechnological innovations.

Keywords: : Zinc oxide nanocomposites, Biomedical applications

INTRODUCTION

Zinc oxide (ZnO) nanocomposites have gained attention in recent years due to their remarkable versatile synthesis approaches, physicochemical properties and wide-ranging applications across various fields. ZnO, a well-known semiconductor with a wide bandgap (3.37 eV) and high exciton binding energy (60 meV), possesses exceptional optical, electrical, and mechanical characteristics, make it suitable for nanocomposite formation. When it is combined with other materials such as polymers, metals, metal oxides, and carbon-based nanostructures, ZnO nanocomposites exhibit enhanced functionality, improved stability, and tailored properties suitable for advanced technological applications [1-7]. The synergy between ZnO and other components enables superior photocatalytic efficiency, antibacterial activity, enhanced electrical conductivity, and mechanical robustness, which are high application in biomedical, environmental, and energy-releted devices [8]. The synthesis of ZnO nanocomposites involves various techniques, ranging from chemical and physical methods to green synthesis approaches, each offering distinct advantages in terms of particle size control, morphology, and crystallinity. Chemical methods such as sol-gel synthesis, hydrothermal and solvothermal techniques, co-precipitation, and chemical vapor deposition allow for precise tuning of the nanocomposite's structural and functional attributes. Physical methods, including sputtering, laser ablation, and mechanical milling, provide alternative routes for fabricating ZnO-based hybrid structures with controlled nanoscale features. Furthermore, the emergence of eco-friendly synthesis techniques using plant extracts, microorganisms, and bio-molecules has revolutionized nanomaterial fabrication, reducing toxic byproducts and promoting sustainable nanotechnology. The choice of synthesis method plays a crucial role in determining the physicochemical characteristics of ZnO nanocomposites, influencing their effectiveness in

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diverse applications [9-13]. ZnO nanocomposites has applications in numerous sectors such as healthcare, electronics, environmental remediation, and energy storage. Their antibacterial and antifungal properties make them promising role for biomedical applications, such as drug delivery systems, wound healing materials, and antimicrobial coatings. In electronics and optoelectronic devices, ZnO-based nanocomposites are employed in sensors, transistors, and light-emitting diodes due to their superior electron mobility and optical transparency. [14-17] The photocatalytic efficiency of ZnO composites has been widely explored for environmental applications, especially in wastewater treatment, air purification, and degradation of organic pollutants. Additionally, ZnO nanocomposites play a significant role in energy storage and conversion, where they are integrated into lithium-ion batteries, supercapacitors, and solar cells to enhance energy efficiency and durability. The multifunctional nature of ZnO nanocomposites has attraction in research efforts toward their development and optimization for next-generation technologies [18-20]. This review provides an in-depth analysis of ZnO nanocomposites, focusing on their key applications of zinc oxide. Furthermore, the diverse range of applications of ZnO nanocomposites will be explored, emphasizing their role in emerging technologies and potential future advancements. By examining the latest research trends and technological innovations, this review aims to highlight the significance of ZnO nanocomposites as a crucial component in modern nanotechnology and materials science.

2. Applications of ZnO Nanocomposites

2.1 Supercapacitors

Supercapacitors have gained attention as a novel type of energy storage system due to their rapid charge-discharge capabilities, extended operational life, and high-power output. They are particularly useful in backup energy systems, hybrid electric vehicles for sustainable transportation, and emergency power supplies. Nanocomposites with high specific capacitance and durability are commonly employed in supercapacitor production, as the nanoparticles (NPs) reduce ionic diffusion distances and thus minimize energy loss. Supercapacitors are generally divided into two categories: electrical double-layer capacitors (EDLCs) and pseudocapacitors. EDLCs store energy through electrostatic charge accumulation at the electrode surface, whereas pseudocapacitors store energy both at the surface and within the bulk of the electrode through a combination of double-layer formation and faradaic (redox) reactions. As a result, pseudocapacitors can store 10 to 100 times more charge compared to EDLCs. Carbon-based materials are typically used for EDLCs due to their excellent electrical conductivity and mechanical properties, although they suffer from relatively low capacitance. In contrast, pseudocapacitors made from conducting polymers and transition metal oxides can achieve higher specific capacitance, but often face challenges with cycling stability. [21-25] Among conducting polymers, polyaniline (PANI) stands out for its cost-effectiveness, environmental resilience, simple synthesis, and favorable doping/ dedoping characteristics. However, PANI is prone to structural degradation during repeated charge-discharge cycles, which limits its stability. This issue is often mitigated by forming nanocomposites or hybridizing with inorganic materials. Other conducting polymers like polypyrrole (PPy) and poly (3,4-ethylene dioxythiophene) (PEDOT), which also undergo redox reactions, are under investigation for their potential in energy storage systems [26]. Zhang et al. [27,28] developed a supercapacitor featuring a carbon nanotube (CNT)–ZnO nanocomposite electrode paired with a PVA–phosphomolybdic acid (PMA) gel electrolyte. The ZnO nanodots were applied to CNT films using ultrasonic spray pyrolysis. To further improve performance, CNTs were printed onto alloy substrates via screen printing, yielding superior results with the PVA-PMA electrolyte. Electrochemical evaluation using cyclic voltammetry (CV) was performed on sheath electrodes composed of ZnO nanorods coated with PPy, and the performance was compared to etched PPy nanotube electrodes. CV scans at 5 and 10 mV/s demonstrated rectangular, symmetrical profiles without distinct redox peaks, indicating excellent capacitive behavior. The current response from the PPy nanotube electrodes surpassed that of the ZnO nanorod-PPy configuration and further improved after 4 hours of etching, which exposed the internal surface of the nanotubes to ionic access, enhancing performance [29]. Multiple researchers have utilized graphene/ZnO hybrid nanocomposites and various nanocomposite as electrodes along with different electrolytes. [30-35], ZnO/ZnS nanoparticles were successfully integrated into supercapacitor electrodes by Zhang et al. [36], enhancing device performance. Chee et al. [38] also demonstrated improved results using a nanocomposite of PPy, graphene oxide (GO), and ZnO as an electrode. Collectively, these studies underscore ZnO's effectiveness in supercapacitor fabrication, particularly when incorporated into appropriate hybrid nanostructures.

2.2 Piezoelectric ZnO/polymer nanocomposites

The global shift toward clean and renewable energy sources is largely driven by volatile oil prices, the depletion of fossil fuel reserves, and the escalating threat of climate change caused by greenhouse gas emissions. Among the emerging alternatives, energy harvesting technologies have gained prominence for their ability to convert ambient energy from external sources into usable forms such as sound, vibration, or electricity. Presently, a variety of energy harvesting methods are being employed, with the most common sources being light, heat, mechanical vibrations, and radio frequency. ZnO/polymer nanocomposites have proven especially effective in photovoltaic and piezoelectric energy harvesting applications [39]. Piezoelectric materials produced electrical energy when subjected to mechanical stress. These materials span several categories, including biological substances (e.g., bone, wood, silk, DNA, RNA), naturally occurring crystals (e.g., Rochelle salt, quartz), ceramics (e.g., lead zirconate titanate, barium titanate, potassium niobate, lithium tantalate), and polymers (e.g., polyvinyl fluoride, synthetic polypeptides, PVDF, aromatic polyamides). Lead zirconate titanate is widely used for harvesting mechanical energy via piezoelectric effect; however, its practical use is limited by brittleness, reliability concerns, safety issues, and long-term sustainability [75]. ZnO-based piezoelectric materials, by contrast, offer better mechanical strength, chemical stability, high sensitivity to small vibrations, and overall efficiency [40,41]. According to Ramadan et al. [42], polymers used in piezoelectric energy harvesting can be classified into three main categories: solid (bulk) polymers with inherent piezoelectric properties in their molecular structure; void-charged polymers, where internal dipoles are created by introducing gas voids and charging surfaces; and polymer composites, where piezoelectric materials like ZnO are incorporated into flexible polymer matrices. The composite approach combines the mechanical flexibility of polymers with the functional benefits of piezoelectric particles, making it particularly promising for scalable and adaptable energy harvesting systems [42]. In this process, the piezoelectric material is typically dispersed in a polyelectrolyte solution and thin films are fabricated by solvent evaporation. Loh et al. [43] explored ZnO loadings between 0% and 60% in poly (sodium 4-styrenesulfonate) and PVA. Their results indicated that higher ZnO content enhanced both piezoelectricity and dynamic strain sensitivity. Notably, films with 50–60 wt% ZnO showed comparable performance to traditional PVDF-based films without the need for high-voltage poling or mechanical stretching [44]. Briscoe et al. [45] fabricated nanogenerators (NGs) using ZnO nanorods in PMMA and PEDOT: PSS matrices and achieved favorable power outputs, particularly for ZnO/PMMA composites. Liu et al. [46] developed a self-powered energy storage system using ZnO/aluminum nanocomposites and UV-curable resin, confirming that ZnO/polymer composites are scalable, cost-effective, and capable of delivering high-output energy harvesting. The development of environmentally friendly piezoelectric materials is also an active area of research. Mun et al. [47] enhanced the piezoelectric response by coating cellulose films with ZnO, achieving charge constants 3.5 to 5 times higher than uncoated cellulose EAPap and PVDF. ZnO/polymer composites not only improve energy conversion efficiency but also offer better mechanical flexibility and integration potential for practical nanogenerator designs. For example, one such NG with a 10 cm × 10 cm area produced an output of ~180 V and ~50 µA under 30 mm of horizontal bending. Performance could be further improved through increased active area or vertical stacking. These NGs demonstrated consistent performance over repeated mechanical cycles, indicating strong reliability and reproducibility. Ou et al. [48] developed a cost-effective ZnO-nanoporous polycarbonate structure using a template-assisted hydrothermal method. This system achieved an energy conversion efficiency of around 4.2% and a peak output power density of approximately 1600 mW/m³ at a load resistance of 1 MΩ, which is in line with performance seen in ZnO nanowire systems. Additionally, several other studies have concentrated on fabricating ZnO/polymer nanocomposite-based piezoelectric materials for enhanced energy harvesting performance [49–50]. Joshi et al. [51] investigated ZnO thin films deposited on different substrates like Phynox, aluminum, Kapton, and Mylar cantilevers. Their results indicated that ZnO films on Phynox generated the highest voltage (~128 mV), attributed to a superior d piezoelectric coefficient of 4.72 pm/V. The piezoelectric coefficient remains a crucial metric for assessing material performance, and numerous investigations have focused on quantifying it in various ZnO-based systems [52, 53].

2.3. Sensors

Conducting polymer nanocomposites have been extensively studied as promising materials for sensor applications due to their impressive sensitivity, fast response and recovery times, stability, durability, and selectivity. The inclusion of nanoparticles (NPs) significantly improves these characteristics, which is essential for potential commercialization. However, challenges still exist in terms of selectivity and long-term durability, particularly in real-world environments that differ from controlled laboratory settings. For example, PANI/ZnO composites have demonstrated effective methanol vapor detection at room temperature, with excellent repeatability and reversibility. The sensor's voltage increased upon methanol exposure and returned to baseline in nitrogen, thanks to the porous, fibrous microstructure of the composite formed by PANI, which enabled better detection than pure ZnO [54]. Similarly, PANI/tin oxide nanocomposites have been investigated for their ability to detect aqueous ammonia [55]. Various molecular interactions—such as hydrogen bonding, chemical bonding, and Van der Waals forces—between PANI and adsorbed vapor molecules contribute to changes in conductivity, which increases in acidic environments and decreases in basic ones. Upon exposure to aqueous NH_2, the sensor’s resistance changed significantly, with response times ranging from 1–7 minutes and a recovery time of 14 minutes. The sensing response was faster at higher ammonia concentrations (30%). NH_3 detection using P3HT:1.00 mol% Au/ZnO nanocomposite films was explored by Kruefu et al. [56]. These composites outperformed neat P3HT, pure Au/ZnO, and other variations in detecting NH_2 over other gases like ethanol, CO, H_2S, NO_2, and water vapor, primarily due to the catalytic activity of Au/ZnO NPs and the porous blend morphology. PANI/ZnO composites have also been utilized for detecting aqueous HCl vapors at various concentrations (10–30%) [57]. Upon exposure, resistance decreased due to deprotonation, which transitioned PANI from its emeraldine salt to the emeraldine base state, lowering hole density and increasing resistance [58]. The PANI/ZnO composite exhibited superior sensitivity and repeatability to both ammonia and HCl vapors when compared to pure PANI, attributed to its porous structure [59]. PPy-based sensors have also been fabricated by incorporating ZnO into the polymer matrix via electropolymerization on platinum substrates. ZnO enhanced the electropolymerization process and facilitated easier formation of the initial polymer layers compared to pure PPy [60]. Humidity sensors using ZnO/PANI nanocomposites have shown substantial changes in resistance and impedance due to water adsorption, which enables directional ion conduction. These composites displayed three times better performance than PANI alone [61]. Flexible photodetectors made from ZnO-10/PET composites exhibited high sensitivity, quick response and recovery times, good orientation, reproducibility, and reliable photoresponse across various UV intensities. These sensors-maintained performances even after mechanical bending, indicating strong structural stability [62]. Pressure-sensitive ZnO nanowire–PMMA composites were examined by Chen et al. [63]. Using a 1 cm^2 sensing area, a small weight produced initial dielectric constant and capacitance values of 6.38 and 90.42 pF, respectively. The electrical and dielectric behavior varied based on polymer matrix and nanoparticle type. ZnO-PSS/PVA thin films, tested under varying dynamic strain, exhibited voltage generation characteristic of strain-sensing behavior due to mechanical deformation. The resulting piezoelectric potential depended on the magnitude of vibrations and was tied to the piezoelectric coefficient [64]. Electrochemical polymerization was used by Kaitsuka and Goto [65] to fabricate PANI/ZnO/PVA double-layer humidity sensors. An increase in ZnO content led to a corresponding decrease in resistance, demonstrating improved sensitivity. This sensitivity was measured as the resistance ratio between dry (20% relative humidity) and target humidity conditions [109]. The presence of ZnO enhanced the charge transfer in PANI, resulting in a distinct water vapor response. Similar humidity sensors using PANI/ZnO composites have been widely reported [66,67]. The photoconductive behavior of ZnO nanobelts (NBs) functionalized with various polymers, such as PSS, PS-co-Mac, PNIPAM, and CMC, has also been analyzed [68]. Upon UV exposure, the conductance of PSS-coated ZnO NBs increased by a factor of 75,000—substantially higher than other polymer-coated counterparts. This enhancement is attributed to the coupling effect between ZnO and PSS, where photon-generated holes are trapped, reducing recombination and extending carrier lifetime. The UV absorption spectrum of PSS showed a peak near 260 nm, closely matching the applied UV wavelength of 280 nm, thus supporting efficient energy absorption and conversion.

2.4. Bioimaging

Zinc oxide (ZnO) quantum dots (QDs) produced through conventional synthesis methods often suffer from limitations such as low quantum yield and broad photoluminescence spectra. Furthermore, their stability in aqueous environments is compromised due to water molecules displacing organic protective ligands on their surfaces. This process disrupts luminescent centers and promotes aggregation, leading to fluorescence quenching. To overcome these issues, surface modification using ligands like polyethylene glycol methyl ether (PEGME), PEG(COOH)$_2$, polyvinylpyrrolidone (PVP), and oleic acid (OA) in combination with diethanolamine (DEA) has been employed [69]. In 2023, Wanas et al. introduced a graphene/folic acid-zinc oxide (GN/FA-ZnO) nanocomposite aimed at dual-mode emission for cancer bioimaging. This nanocomposite demonstrated low toxicity, strong photostability, and dual-mode luminescence, with emissions visible to the naked eye and extended luminescence lifetime. In vivo imaging in mice bearing Ehrlich tumors confirmed its targeted bioimaging capabilities [70]. Similarly, Hing et al. synthesized green fluorescent ZnO nanowires that proved effective for targeted imaging of cancer cells. When labeled with Cu for PET imaging in healthy mice, the nanowires predominantly accumulated in the liver. Surface functionalization of these ZnO nanowires improved water solubility, biocompatibility, and reduced toxicity, enhancing their potential for optical cancer imaging. In another approach, red fluorescent ZnO nanoparticles were created by conjugating Cu and TRC105 to the nanoparticles. These exhibited effective tumor targeting, as PET imaging revealed significant radioactivity in the liver, tumor, and abdominal regions, with TRC105 playing a key role in tumor uptake enhancement [71]. Xiong et al. utilized a two-step polymerization process to develop luminescent ZnO/poly(MAA-co-PEGMEMA) hybrids with customizable photoluminescence suitable for cell imaging. These hybrids maintained stable emissions during cell culture and showed green and yellow fluorescence. Cytotoxicity assessments indicated over 90% cell viability at ZnO QD concentrations below 0.2 mg/mL, demonstrating their suitability for bioimaging due to their controlled luminescence and low toxicity [72]. Earlier, in 2013, researchers synthesized ZnO nanoparticles using bases like NaOH, KOH, and LiOH, yielding a range of emission colors including blue, green, cyan, and orange. Among these, LiOH proved to be the most effective in modulating ZnO nanoparticle emission properties depending on its concentration [73].

2.5. Antimicrobial Properties

Zinc oxide (ZnO) nanoparticles exhibit strong antimicrobial potential against a wide range of pathogens. Their mode of action includes both bactericidal and fungicidal effects, meaning they not only inhibit the growth of microorganisms but also prevent them from forming new colonies [74,75]. Cierech et al. investigated the antifungal capabilities of ZnO nanoparticles against *Candida albicans* and explored their integration into polymethyl methacrylate (PMMA) resin. The study utilized ZnO nanopowder with an average size of 30 nm, and ultrasonic treatment was applied to reduce particle agglomeration in the resin solution by a factor of 11. This indicated effective incorporation of ZnO NPs into the composite, suggesting the need for further studies to enhance dispersion uniformity and evaluate its antimicrobial performance, mechanical properties, and biocompatibility for possible clinical applications [76]. Although the precise mechanisms behind ZnO's antimicrobial action are not fully established, several research efforts have identified likely pathways.

These include: (a) disrupting bacterial membranes leading to cell death [77], (b) generating reactive oxygen species (ROS) within bacterial cells via photocatalytic activity [78,79], and (c) releasing Zn^{2+} ions, which damage essential cellular macromolecules such as DNA and proteins. The effectiveness of these mechanisms is largely influenced by both the concentration and particle size of the ZnO nanoparticles. Smaller particles have been shown to be more effective, indicating a size-dependent enhancement in antimicrobial performance [80].

2.6. Applications of ZnO-Based Nanocomposites for Vaccines and Immunotherapy

Eliciting a robust immune response against protein antigens requires several coordinated steps, including the efficient delivery of antigens to antigen-presenting cells (APCs)—especially dendritic cells—and their effective processing and presentation to T cells. An ideal vaccine platform must facilitate antigen delivery, activate dendritic cells, and direct T cell differentiation toward desired immune responses. The rise in nanotechnology-based vaccines, which vary in their composition, shape, size, and surface characteristics, underscores the progress in this field and the increasing number of such platforms either approved or under clinical evaluation [81,82]. Cho et al. developed core–shell nanoparticles composed of iron oxide and zinc oxide that serve dual functions: delivering carcinoembryonic antigen (CEA) to dendritic cells and acting as imaging agents. These nanoparticles are readily internalized by dendritic cells and can be tracked using confocal microscopy and magnetic resonance imaging. Immunization of mice with dendritic cells loaded with these nanoparticles led to stronger tumor-specific T-cell responses, reduced tumor growth, and improved survival outcomes compared to controls [83]. In 2017, another study examined the anticancer efficacy of poly I:C (pIC) RNA bound to unmodified ZnO nanoparticles for melanoma treatment. The direct binding of RNA to ZnO nanoparticles was confirmed through changes in particle size, zeta potential, and optical spectra, with transmission electron microscopy (TEM) used to visualize the RNA coating. This nanoparticle-RNA complex induced pronounced cell death in human (A375) and mouse (B16F10) melanoma cell lines and significantly inhibited tumor progression in a mouse melanoma model. Further analysis of tumor tissue revealed changes in key signaling proteins and upregulation of inflammatory markers such as IL-6 and IFN-γ. Proteomic profiling revealed unique signatures associated with both ZnO and pIC, suggesting the platform’s potential in cancer immunotherapy [84]. Additionally, in 2019, Sharma et al. demonstrated the use of ZnO-based nanocomposites for vaccine delivery using radially oriented ZnO nanowires grown on poly-l-lactic acid (PLLA) microfibers. This 3D hybrid scaffold exhibited minimal cytotoxicity while effectively delivering tumor antigens to dendritic cells. These cells subsequently showed increased expression of inflammatory cytokines and activation markers. The composite triggered robust tumor-specific immune responses, significantly slowing tumor growth in vivo. Moreover, this system reduced regulatory T cells (TRegs) and increased the infiltration of T cells into tumor tissue, pointing to its promise as a next-generation vaccine delivery system using inorganic–organic nanocomposites [85].

2.7. ZnO Nanocomposites as an Antigen Delivery System

A vital component of effective antigen presentation by antigen-presenting cells (APCs) to $CD4^+$ and $CD8^+$ T cells via MHC class II and I pathways, respectively, is the method by which the antigen is delivered [130]. While several cellular pathways are involved in processing both exogenous and endogenous antigens, those routed through endocytic or phagocytic systems typically result in MHC class II presentation to $CD4^+$ T cells. In contrast, antigens present in the cytosol are processed through the proteasome and presented via MHC class I molecules to $CD8^+$ T cells [86,87]. Therefore, ensuring that antigens are accurately delivered to the appropriate intracellular compartments is critical for eliciting specific and robust T cell responses. Previous research by the authors’ group demonstrated that ZnO nanocomposites can efficiently deliver antigens to both the endosomal and cytosolic compartments, leading to a notable increase in both $CD4^+$ and $CD8^+$ T cells reactive to ZnO-associated antigens [88,89,90]. When antigens are conjugated to zinc-binding peptides (ZBPs), they can be internalized not only via phagocytosis but also through direct entry into the cytosol, possibly by penetrating the cell membrane directly [91,92,93]. Additionally, studies showed that ZnO nanoparticle-associated peptide antigens localize with lysosomes in dendritic cells within hours of incubation, confirming effective uptake [94]. Hollow ZnO nanospheres loaded with ovalbumin (OVA) significantly improved antigen uptake by APCs in vitro [95]. Moreover, the intracellular delivery of peptides via fan-shaped ZnO nanowires (NWs) was observed even at 4°C—when endocytic activity is suppressed—indicating membrane penetration as a likely route of entry [96]. These 3D ZnO nanostructures were also capable of delivering DNA into cells, with successful gene expression, suggesting transient membrane and possibly nuclear penetration [97]. Similar delivery and expression of plasmid DNA using ZnO tetrapods has been reported in other studies [98]. Given that ZnO nanocomposites are known to stimulate autophagy—an intracellular degradation pathway linked to both MHC class I and II presentation—they may further enhance antigen processing and presentation, although this potential remains to be fully validated in APCs [99]. Overall, ZnO-based nanocomposites show considerable promise for delivering antigens to both endocytic and cytosolic compartments, thereby boosting antigen presentation via both MHC pathways.

2.8. Induction of Antigen-Specific Adaptive Immunity by ZnO Nanocomposites Challenges

When antigens are presented by antigen-presenting cells (APCs) in secondary lymphoid organs, CD4$^+$ T cells become activated and differentiate into specific subtypes—including TH1, TH2, TH17, and TFH cells—each contributing to distinct aspects of adaptive immunity [100]. This differentiation process is influenced by the cytokine environment, the nature of the APCs involved, antigen concentration, and the presence of co-stimulatory signals [101]. Each CD4$^+$ T cell subset is characterized by a unique cytokine profile: (i) TH1 cells produce IFN-γ, which activates monocytes/macrophages and supports CD8$^+$ T cell proliferation through IL-2; (ii) TH2 cells secrete IL-4, IL-5, and IL-13, which are involved in humoral and allergic immune responses; (iii) TH17 cells release IL-17 and IL-22, mediating inflammation and tissue protection; and (iv) TFH cells express IL-21 and facilitate B cell function through immunization. This was evidenced by increased levels of OVA-specific IgG1 and IgE antibodies and heightened secretion of IL-4 and IL-5, while TH1 responses, indicated by IFN-γ and IgG2a, were less pronounced. Additionally, IL-17 production was elevated in splenocytes, suggesting some induction of TH17 responses [102]. However, other studies using different ZnO nanocomposite formulations—including those with high-affinity zinc-binding peptide (ZBP)-fused antigens—showed significant enhancement of TH1 and CD8$^+$ T cell responses in C57BL/6 mice. These effects were observed in experiments involving immunization with antigen-loaded dendritic cells or direct subcutaneous administration of the antigen-nanoparticle complex [91,92,93]. Further investigations demonstrated robust antigen-specific cellular immunity, marked by increased cytotoxic T lymphocyte (CTL) activity, elevated IFN-γ-producing CD4$^+$ and CD8$^+$ T cells, and a higher IgG2a/IgG1 ratio in mice immunized with ZnO tetrapods [103], mesoporous ZnO nanocapsules [104], and Zn-doped mesoporous silica nanoparticles [105]. These findings indicate that ZnO nanocomposites can effectively promote TH1-type and cell-mediated immune responses, though outcomes may vary depending on the nanocomposite design, adjuvant formulation, immunization method, and host genetic background. Continued research is necessary to refine these parameters and optimize antigen-specific T cell and antibody responses for different therapeutic targets.

2.9. Remaining Challenges

While ZnO nanocomposites show strong potential as immune-modulating agents, several obstacles must be addressed before they can be used as ready-to-use, adjuvant-like materials. One of the primary challenges lies in the large-scale production of uniform ZnO nanocomposites with the desired therapeutic properties. In physiological aqueous environments, these nanocomposites often struggle to maintain stability and tend to aggregate. Enhancing their stability typically requires surface modifications using polymers such as PEG, chitosan, or other organic and inorganic substances. Therefore, additional functionalization steps are essential to make ZnO nanocomposites viable for biomedical applications. Interestingly, stability in aqueous systems can be improved by conjugating poly(I:C) to ZnO nanoparticles through electrostatic interactions between the positively charged ZnO and negatively charged double-stranded RNA. Combining inorganic (ZnO) and organic (poly(I:C)) components may lead to enhanced therapeutic effects in vaccine delivery and immunotherapy systems [106]. Moreover, the various physicochemical features of ZnO nanocomposites—such as size, three-dimensional structure, composition, and surface modifications—can significantly influence their interaction with biological systems both in vitro and in vivo. This highlights the need to establish a fundamental understanding of the nano-bio interaction mechanisms specific to ZnO materials. Although many studies focus on synthesizing different shapes and sizes of ZnO through facet-controlled methods, there is a growing need to explore how these facet-specific properties impact biological interactions. Such investigations could greatly contribute to advancing ZnO's biomedical applications. costimulatory interactions [107]. Research has shown that ZnO-based nanocomposites can modulate immune responses and support the differentiation of $CD4^+$ T cells and antibody production when co-administered with specific antigens [91,92,108-110]. For instance, one study using 21 nm ZnO nanoparticles combined with ovalbumin (OVA) antigen demonstrated a pronounced TH2-biased immune response in DBA/IJ mice following intraperitoneal

CONCLUSION

Zinc oxide (ZnO) nanocomposites represent a rapidly evolving class of advanced materials with wide-ranging applications across biomedical, environmental, and technological fields. Their exceptional physicochemical properties—such as high surface area, semiconducting behavior, photocatalytic activity, and biocompatibility—make them ideal for multifunctional applications. This review has highlighted various synthesis techniques, including sol-gel, hydrothermal, and green synthesis methods, which offer versatility in tailoring morphology and improving dispersion within matrices. ZnO nanocomposites have demonstrated remarkable performance in areas like antimicrobial coatings, drug delivery systems, photocatalysis for pollutant degradation, energy harvesting, supercapacitors, and biosensors. Additionally, their role in emerging fields such as vaccine delivery and immunotherapy underscore their potential in precision medicine. However, despite significant progress, challenges remain—particularly in achieving large-scale, cost-effective, and reproducible synthesis, controlling particle agglomeration, and understanding long-term biocompatibility and environmental safety. Addressing these limitations requires an interdisciplinary approach that integrates nanotechnology, materials science, biology, and environmental engineering. Future research should focus on optimizing fabrication methods, enhancing the stability and targeted functionality of ZnO nanocomposites, and exploring their interactions at the nano-bio interface. With continued innovation and rigorous evaluation, ZnO nanocomposites are poised to play a transformative role in next-generation technologies and sustainable development.

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