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LEVERAGING DOPED ZINC OXIDE NANOPARTICLES FOR ADVANCEMENTS IN SKIN CANCER THERAPY

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Abstract

Skin cancer remains a formidable challenge in modern oncology, ranking as the fifth most prevalent malignancy globally. Conventional therapeutic strategies for early-stage skin cancer predominantly include surgical excision, Mohs micrographic surgery, radiation therapy, curettage with electrodessication, cryotherapy, and photodynamic therapy. While chemotherapy remains a cornerstone in cancer treatment, it is often hindered by several limitations, including inadequate therapeutic efficacy, the development of tumor resistance, poor solubility and permeability, as well as systemic toxicity. In recent years, the advent of nanotechnology has revolutionized biomedical research, particularly in oncology, by offering innovative approaches to improve drug delivery, enhance tumor targeting, and optimize therapeutic outcomes. Among various nanomaterials, nanoparticles (NPs) have emerged as promising candidates for skin cancer treatment due to their unique physicochemical properties, high biocompatibility, and ability to achieve targeted drug delivery with minimal off-target effects. Zinc oxide (ZnO) nanoparticles, in particular, have garnered substantial attention for their potent anticancer properties, which can be further enhanced through doping strategies to improve their efficacy, stability, and selectivity against malignant cells. This review comprehensively examines the therapeutic potential of doped ZnO nanoparticles in skin cancer treatment.

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Introduction

Cancer remains one of the most significant causes of death worldwide, presenting a major obstacle to improving life expectancy [1]. According to the World Health Organization (WHO), approximately 10 million people lost their lives to cancer in 2020. Projections suggest that by 2040, the number of new cancer cases diagnosed each year will rise to 29.5 million, with annual cancer-related deaths reaching 16.4 million. Despite remarkable advancements in medical research, technology, and treatment strategies, cancer remains a challenging disease due to its ability to grow and spread uncontrollably [2]. Under normal conditions, cell division is strictly regulated to maintain healthy tissue function. However, cancer develops when these regulatory processes break down, leading to unchecked cell proliferation. In the early stages, cancerous cells may behave similarly to normal cells, but as they continue to divide uncontrollably, they acquire the ability to generate their own blood supply, detach from their original site, and spread to other parts of the body [3]. This aggressive and invasive nature makes cancer life-threatening, as malignant cells evade the body's built-in regulatory signals that typically limit cell growth. Unlike normal cells, which divide only when necessary, cancer cells undergo uncontrolled replication due to genetic mutations that disrupt essential cellular checkpoints, driving the progression of the disease [4].

Skin cancer is generally categorized into two main types: nonmelanoma skin cancers (NMSCs) and melanoma. NMSCs primarily consist of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Among these, SCC is more frequently seen in individuals with darker skin tones, whereas BCC is most commonly diagnosed in people of European descent. Exposure to radiotherapy increases the risk of BCC, whereas human papillomavirus (HPV) infection has been linked to SCC. Although melanoma is less common in India compared to NMSCs, it is significantly more aggressive. Early detection and

treatment of melanoma can lead to successful outcomes, but delayed intervention facilitates metastasis, complicating therapeutic efforts. In 2018, global reports estimated 18.1 million new cases of skin cancer and 9.6 million associated deaths [5-6]. Additionally, the Global Burden of Disease Study (2015) provided valuable insights into melanoma incidence, mortality rates, and disability-adjusted life years (DALYs), offering a comprehensive perspective on the disease burden across different regions [7].

Current treatment strategies for early-stage skin cancer primarily include excision surgery, Mohs surgery, radiation therapy, curettage and electrodesiccation, cryotherapy, and photodynamic therapy. However, in advanced stages where surgical and radiation-based interventions are ineffective, alternative treatments such as immunotherapy, targeted therapy, and chemotherapy are employed. Even after surgical or radiation treatment, these approaches help prevent recurrence. Despite their therapeutic benefits, immunotherapy and targeted therapy are often hindered by high costs and limited bioavailability, making chemotherapy a more accessible option. However, chemotherapy has notable limitations, including low therapeutic efficacy, tumor resistance, poor solubility and permeability, and systemic toxicity [8-9]. According to the American Cancer Society, the five-year survival rate for melanoma that has spread to regional lymph nodes is approximately 68%, while distant metastasis reduces the survival rate to around 30%. These statistics underscore the urgent need for innovative therapeutic approaches to enhance patient outcomes, particularly for advanced-stage skin cancer [10].

Nanotechnology has gained significant traction in biomedical research, especially in oncology, due to its potential to manipulate materials at the nanoscale (1–1000 nm) [11]. Nanomaterials exhibit unique physicochemical properties that enhance cancer treatment efficacy. Their advantages include (1) size compatibility with biomolecules, enabling direct biological interactions, (2) improved solubility, which can be optimized through surface modifications, (3) a high surface area-to-volume ratio, allowing efficient drug encapsulation and delivery, and (4) selective targeting capabilities that minimize collateral damage to healthy tissues [12]. Beyond oncology, nanomedicine is also being explored for personalized medicine and dermatological applications. Various nanomaterials, including nanofibers, nanosuspensions, nanoemulsions and nanoclays have demonstrated promise in skin cancer treatment. Nanomaterials play a crucial role in the treatment of skin cancer, with nanoparticles (NPs) receiving significant attention due to their unique characteristics. These include passive tumor targeting through the enhanced permeability and retention (EPR) effect, the ability to evade the reticuloendothelial system (RES), and improved skin permeability [13-14]. Nanoparticles can be broadly categorized into three main types: inorganic NPs, polymer-based NPs, and lipid-based NPs. Inorganic NPs are particularly noteworthy as they function both as drug carriers and therapeutic agents, whereas polymer and lipid-based NPs are primarily designed to enhance drug delivery in a controlled manner, improving permeability through the skin and tumor tissues [20-22]. Among these, nanoparticles (NPs) have shown superior efficacy due to their dual functionality as both therapeutic agents and drug carriers. Their ability to encapsulate hydrophilic and lipophilic drugs, facilitate tumor targeting via active or passive mechanisms, overcome chemoresistance, regulate drug release, and enhance skin permeability makes them highly promising for skin cancer therapy. Despite its immense potential, nanotechnology in oncology is still evolving, with only a limited number of nanoparticle-based treatments receiving regulatory approval. Notable FDA-approved nanomedicines include Doxil® (PEGylated liposomal doxorubicin, 1995), Abraxane® (albumin-bound paclitaxel, 2005), Oncaspar® (polymer-protein conjugated L-asparaginase, 2006), Marqibo® (liposomal vincristine, 2012), Onivyde® (liposomal irinotecan, 2015), and Vyxeos® (liposomal cytarabine/daunorubicin, 2017). Similarly, the European Medicines Agency (EMA) has approved inorganic''' nanoparticles such as NanoTherm® (iron oxide nanoparticles, 2010) and Hensify® (hafnium oxide nanoparticles, 2019). However, most of these formulations have been developed for treating cancers such as breast cancer, ovarian cancer, non-small cell lung carcinoma, sarcoma, glioblastoma, pancreatic cancer, leukemia, and multiple myeloma, with limited applications in skin cancer [15-19]. This review explores the use of doped ZnO nanoparticles in treatment of skin cancer.

Zinc Oxide Nanoparticles

Zinc oxide nanoparticles (ZnO NPs) have garnered significant attention in nanomedicine due to their unique physicochemical properties, making them promising candidates for drug delivery, cancer diagnosis, and treatment. Their biocompatibility, low toxicity, and ability to generate reactive oxygen species (ROS) contribute to their effectiveness as antimicrobial, anticancer, anti-inflammatory, and antioxidant agents. ZnO NPs are also being explored for use in wound healing, bio-imaging, and theranostics [23-26]. The versatility of ZnO NPs in medicine stems from their ability to act as nanocarriers for targeted drug delivery. Their high surface area-to-volume ratio allows for efficient drug loading and controlled release, improving therapeutic efficacy while minimizing side effects. Notably, ZnO NPs exhibit pH-sensitive behavior, dissolving readily in the acidic tumor microenvironment, thereby enabling selective drug release at the target site. This characteristic makes them particularly suitable for tumor-targeted therapies. Furthermore, ZnO NPs have demonstrated potential in combating bacterial and viral infections. Their anticancer activity is attributed to the generation of ROS, leading to oxidative stress and bacterial cell membrane disruption [27]. Due to their antimicrobial properties, ZnO nanoparticles (ZnO NPs) have emerged as promising materials for coating medical implants, helping to minimize the risk of infections following surgery. Researchers are also investigating their antiviral capabilities for potential use in vaccine adjuvants and antiviral drug formulations. The global market for ZnO NPs is expected to expand significantly, with projections indicating an increase of approximately $1.3 billion over six years. This growth suggests a rise in market value from $4.4 billion in 2019 to an estimated $5.7 billion by 2024.

The increasing demand for ZnO NPs across multiple industries is a key factor driving this trend, underscoring their growing importance in various applications [28-30]. In cancer treatment, ZnO NPs have demonstrated potential by triggering programmed cell death (apoptosis) in cancer cells through reactive oxygen species (ROS)-mediated pathways. They also enhance the effectiveness of chemotherapy by improving targeted drug delivery and minimizing side effects. Additionally, their role in photodynamic and photothermal therapies is gaining attention, as their strong optical absorption properties allow them to act as photosensitizers, aiding in more effective tumor elimination [31]. Although ZnO nanoparticles (ZnO NPs) hold great potential for biomedical applications, several challenges have limited their widespread clinical use. One of the primary concerns is their instability in biological fluids, which can lead to the uncontrolled release of Zn^{2+} ions, potentially causing toxicity to healthy cells. To mitigate these issues, researchers are investigating doping techniques, where specific elements are integrated into the ZnO crystalline structure to improve stability, enhance therapeutic properties, and minimize adverse effects [32]. Doped ZnO NPs have demonstrated superior optical, electrical, and catalytic characteristics, making them more suitable for medical applications. This approach not only enhances the existing benefits of ZnO NPs but also introduces new functionalities, further expanding their potential in biomedical research and treatment. By incorporating tailored dopants into the ZnO crystalline lattice, researchers have successfully modified and optimized various physical and chemical characteristics, including optical, electrical, electromechanical, and catalytic properties [33-34]. In some cases, doped ZnO nanomaterials have demonstrated entirely new and superior functionalities compared to their undoped counterparts. In addition to biomedical applications, both doped and undoped ZnO NPs have been widely employed as photocatalysts for organic dye degradation. Doped ZnO has demonstrated significantly improved photocatalytic efficiency compared to its pure form [35]. This enhancement is primarily due to a reduced electron-hole recombination rate, which promotes better charge separation and leads to increased photocatalytic activity. Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Union (EU) acknowledge the potential of nanotechnology in advancing medical treatments. The FDA has classified ZnO nanoparticles (ZnO NPs) as "generally regarded as safe" (GRAS), further supporting their development for healthcare applications. However, before they can be widely adopted for human use, extensive preclinical and clinical research is necessary to assess their long-term safety and effectiveness [36-37].

Rare Earth

Rare earth (RE) or lanthanide elements are extensively utilized for doping ZnO nanomaterials, allowing for tailored modifications of their electronic band structure. As noted by Cerrato et al., [44] ZnO exhibits rapid recombination of photogenerated charge carriers under UV light irradiation, limiting its quantum efficiency as a photocatalyst. However, due to their unique 4f electronic configuration, lanthanide elements can extend the recombination time of electron-hole pairs, thereby enhancing photocatalytic efficiency and influencing antimicrobial properties. For instance, cerium doping has been shown to improve the photocatalytic activity of ZnO nanorods, even surpassing titanium dioxide (TiO_2), a conventional photocatalytic benchmark. Beyond photocatalysis, RE doping also impacts the luminescence characteristics of ZnO. By introducing trap states, which act as radiative recombination sites absent in pure ZnO, dopants influence both optical properties and crystallite size, leading to tunable band-gap energies. Kumar et al. [45] highlighted that RE doping enhances ZnO's luminescence due to transitions involving 4f orbitals within the crystal lattice. A study by Zhao et al. demonstrated that terbium-doped ZnO nanotubes exhibited distinct visible-light emission bands at 543 nm, 586 nm, and 620 nm, with the 586 nm emission attributed to energy transfer between ZnO and Tb^{3+} ions. Furthermore, RE doping significantly alters the piezoelectric characteristics of ZnO by introducing defects that intensify the asymmetry of its wurtzite crystalline structure. For example, lanthanum-doped ZnO exhibited ferroelectric properties and an order-of-magnitude increase in the piezoelectric coefficient ($d_{33} \approx$ 101.30 pm/V) compared to bulk ZnO (12.4 pm/V). This enhancement was linked to the larger ionic radius of lanthanum (1.22 Å) relative to zinc (0.74 Å), which induced greater crystal lattice distortion and stronger spontaneous polarization. In addition to piezoelectric and optical modifications, RE elements can also influence ZnO's magnetic properties. While transition metals are typically preferred for inducing room-temperature ferromagnetism (RTFM) in ZnO, gadolinium doping has been shown to successfully introduce magnetic behavior. Specifically, ZnO:Gd films prepared via low-energy ion implantation exhibited RTFM and superparamagnetic clustering after thermal annealing at 650 °C, though the underlying mechanism remains a subject of ongoing investigation [43].

Transition Metal

Among transition metal (TM) dopants, iron is one of the most commonly used due to its ability to exist in two oxidation states, Fe^{2+} and Fe^{3+}. These oxidation states have distinct effects on both the structural and electrical properties of ZnO, primarily due to differences in ionic radius and charge. While research on Fe-doped ZnO has predominantly focused on its magnetic properties, some studies have also highlighted its role in enhancing the chemical stability of ZnO nanoparticles in aqueous environments and improving electromechanical performance. For instance, Srinivasulu et al. [52] reported that increasing iron concentration in ZnO thin films enhances ferromagnetic behavior at room temperature. Additionally, post-synthesis annealing conditions significantly influence the ferromagnetic characteristics of Fe-doped polycrystalline ZnO powders [53]. Specifically, annealing in a hydrogen atmosphere optimized the ferromagnetic response, whereas annealing in an argon atmosphere failed to induce ferromagnetism. However, the underlying mechanisms responsible for these magnetic properties remain unclear, with conflicting explanations in the literature. Regarding piezoelectric properties, Luo et al. [51] emphasized the importance of the oxidation state of Fe ions in ZnO. Their findings indicate that

Fe^{3+}, due to its smaller ionic radius, enhances the piezoelectric coefficient more effectively (~128 pC/N at 1.2 at.% Fe doping) compared to Fe^{2+}, which results in a significantly lower coefficient (9 pC/N). Manganese is another widely studied dopant for ZnO, though controlling its oxidation state presents challenges. Mn doping is primarily investigated for its effects on optical, structural, and magnetic properties. Studies have shown that the ferromagnetic behavior of Mn-doped ZnO depends on doping concentration, but not in a straightforward manner. For example, ZnO with 1 at.% Mn exhibited diamagnetic behavior, while at 5 at.% doping, it became ferromagnetic [46-50]. Similarly, its piezoelectric response varied with Mn concentration. Research by Pan et al. [42] found that the d33 piezoelectric coefficient initially decreased with Mn doping up to 4.8 at.% but increased with higher concentrations, a trend attributed to changes in the Mn oxidation state. Since different oxidation states alter ionic radius, they also influence the resistance to oxygen-metal bond rotation within the ZnO lattice. Copper doping, on the other hand, has been explored primarily for enhancing ZnO's antimicrobial properties. Hassan et al. [54] successfully synthesized Cu-doped ZnO coatings that exhibited improved antibacterial efficacy against E. coli under light exposure. This enhancement was linked to increased reactive oxygen species (ROS) generation and the synergistic release of cytotoxic Cu^{2+} and Zn^{2+} ions. Beyond Fe, Mn, and Cu, other TM dopants such as chromium and cobalt have been investigated for their unique effects on ZnO. Cr-doped ZnO films, prepared through reactive magnetron co-sputtering, exhibited enhanced piezoelectric properties and ferroelectric behavior due to the substitution of Zn^{2+} by smaller Cr^{3+} ions, leading to the formation of permanent electric dipoles [48]. Meanwhile, cobalt doping has been shown to increase ZnO's band gap, making it more transparent to visible light, while also inducing room-temperature ferromagnetism in ZnO nanoparticles [53].

Role of Doping In Enhancing ZNO Properties

Zinc oxide (ZnO) is a highly adaptable inorganic material with a broad range of applications, including gas sensing, energy harvesting, and biomedical uses. Instead of solely enhancing its existing properties, introducing new functionalities can transform ZnO into a multifunctional material [38]. One of the most effective ways to achieve this is through doping, where specific ions are incorporated into the ZnO crystal lattice. This modification plays a crucial role in adjusting the material's energy band gap, which directly impacts its photocatalytic performance and antimicrobial properties. Additionally, doping can induce weak ferromagnetic behavior in ZnO nanoparticles, influence their degradation rate in aqueous environments, and modify their electromechanical response [39]. The extent to which doping affects ZnO's physical and chemical properties depends largely on the type of element introduced. Key factors such as ionic radius, electronegativity, and coordination state collectively determine the final characteristics of the modified material. By carefully selecting appropriate dopants, researchers can fine-tune ZnO's performance for specific applications, broadening its potential in both technological and medical fields [40-42].

Methods of Synthesis of Dopped ZnO Nanoparticles

Wet chemical method

Wet chemical methods are widely regarded as one of the most effective approaches for synthesizing micro and nanostructured materials. Their key advantages include the use of environmentally friendly solvents, relatively low synthesis temperatures, and minimal equipment requirements. Additionally, these methods offer high material purity and well-controlled stoichiometry, making them particularly suitable for the fabrication of doped ZnO nanoparticles.

A typical sol-gel/hydrothermal method to prepare ZnO-based materials is based on the following reactions:

$$Zn^{2+} + 2OH^- \rightarrow Zn(OH)_2$$

$$Zn(OH)_2 + 2OH^- \rightarrow Zn(OH)^{2-}{}_4$$

$$Zn(OH)^{2-}{}_4 \rightarrow ZnO + H_2O + 2OH^-$$

Goel et al. [55] explored the synthesis of Gd-doped ZnO nanorods using a wet chemical solution approach, employing zinc chloride and gadolinium (III) chloride hydrate dissolved in distilled water. In their study, a salt solution containing 5 mol.% Gd^{3+} relative to ZnO was gradually introduced into a sodium hydroxide (NaOH) solution to induce precipitation of the desired nanoparticles. Structural characterization through TEM and XRD analyses revealed that Gd incorporation into the ZnO wurtzite crystalline structure occurred without the formation of secondary phases. The study further indicated an increase in the unit cell parameters upon Gd doping compared to pure ZnO nanorods. This expansion was attributed to the larger ionic radius of Gd^{3+} replacing Zn^{2+} within the host lattice, leading to a modified crystal structure. Such distortions enhanced the piezoelectric coefficient from 12.4 pm/V in pure ZnO to a maximum of 45.49 pm/V for the Gd-doped nanoparticles.

In a separate investigation by Selvaraj et al., [56] gadolinium (III) nitrate hexahydrate was used as the doping precursor. This study evaluated the photocatalytic performance of Gd-doped ZnO nanoparticles synthesized via a co-precipitation method. The process involved mixing metal precursors in specific ratios, followed by NaOH addition to facilitate precipitation. Post-synthesis, the samples underwent calcination at 500°C for two hours. XRD analysis indicated that a 5 mol.% Gd doping level resulted in the appearance of a secondary phase, suggesting the solubility limit of Gd^{3+} in this synthesis. FTIR spectroscopy showed a broadening of the Zn—O bond peak (443 cm^{-1}) in doped samples due to lattice distortions. Additionally, a decrease in band-gap energy was observed with increasing Gd concentration up to 3 mol.%, followed by an increase at 5 mol.%, which was attributed to quantum confinement effects associated with reduced crystallite size.

Europium (Eu) doping has also been investigated for enhancing the X-ray absorption properties of ZnO nanoparticles, particularly for applications in cancer radiation therapy. In one study, Eu-doped ZnO nanoparticles were synthesized via chemical precipitation, using zinc acetate and europium (III) nitrate pentahydrate dissolved in methanol, with NaOH facilitating oxide formation. The resulting ZnO:Eu nanoparticles, measuring 8–9 nm in size, demonstrated an increased ability to generate reactive oxygen species under X-ray exposure, outperforming pure ZnO counterparts [57].

Additional research has explored the use of other rare-earth elements such as lanthanum (La) and cerium (Ce) in ZnO doping, employing a sol-gel method. For instance, ZnO nanoparticles were synthesized from zinc nitrate and lanthanum (III) chloride heptahydrate, exhibiting enhanced light absorption properties and successfully serving as photo-anodes in dye-sensitized solar cells. Similarly, Ce-doped ZnO nanorods were fabricated using zinc chloride and cerium chloride. XRD analyses confirmed the effective incorporation of La and Ce dopants into the ZnO lattice, with diffraction peaks shifting toward higher angles compared to undoped ZnO. This shift suggested an increase in crystalline defect density, affirming successful doping [58-59].

Combustion method

Beyond conventional wet chemical methods, combustion-based synthesis techniques have emerged as an alternative approach for the production of doped ZnO nanoparticles. Among these, solution combustion synthesis has been widely investigated. This method involves dissolving the precursors of the desired material such as zinc and dopant element precursors in a fuel like urea, glycine, or citric acid. The resulting solution is then introduced into a preheated muffle furnace at a temperature exceeding the ignition point of the fuel. Once ignited, an exothermic reaction occurs between the fuel and the oxidizing agents present in the solution, leading to the formation of the target oxide along with gaseous byproducts.

Doping ZnO nanoparticles with various elements has been successfully achieved using this technique. Notably, noble metals such as gold and silver have been incorporated into ZnO structures. For instance, Pathak [60] et al. synthesized Ag- and Au-doped ZnO nanoparticles using a solution combustion method. In their study, zinc nitrate hexahydrate was mixed with urea (acting as the fuel) alongside small amounts of silver nitrate or tetrachloroauric (III) acid hydrate as dopants. The solution was preheated to 80°C in 5 mL of water before being placed in a furnace at 500°C to initiate combustion. Unlike sol-gel methods, this approach led to the formation of secondary phases of noble metals, as confirmed by scanning electron microscopy (SEM) and X-ray diffraction (XRD) analyses. Similarly, ZnO nanoparticles have been doped with nickel using solution combustion synthesis. Silambarasan et al. utilized zinc acetate, nickel (II) acetate, ethanol, and ethylene glycol as precursors, which were ignited to obtain the doped ZnO powder. XRD analysis revealed high crystallinity in the synthesized material; however, additional diffraction peaks corresponding to an NiO secondary phase were observed. A comparable issue arose in the synthesis of vanadium-doped ZnO nanoparticles, where zinc nitrate hexahydrate and glycine served as the primary precursors, with ammonium metavanadate (NH_4VO_3) used as the doping agent and water as the solvent. XRD analysis of the resultant powders indicated secondary phase formation, particularly at higher doping concentrations [61-62]. Addressing these challenges, Xia [63] et al. demonstrated that iron-doped ZnO nanoparticles synthesized via flame spray pyrolysis exhibited improved biocompatibility due to reduced Zn^{2+} ion dissolution in biological media. Their method involved dissolving zinc and iron naphthalene in xylene, followed by atomization and combustion in a methane-oxygen flame. The resulting doped ZnO nanoparticles were smaller than their undoped counterparts, and XRD patterns showed no additional peaks apart from the characteristic wurtzite phase, suggesting successful doping without secondary phase formation.

Table 1: Methods of Synthesis [80-87]

Method	Principle	Advantages	Disadvantages
Sol-Gel Method	Involves the transition of a system from a liquid "sol" (mostly colloidal) into a solid "gel" phase.	Simple setup, controllable, cost-effective, relatively low temperatures	Requires calcination, long processing time
Co-Precipitation	Simultaneous precipitation of zinc and dopant ions from a solution, forming a solid precipitate.	Simple, low cost, good purity.	Possible agglomeration, requires precise control over conditions
Hydrothermal Method	Chemical reactions occur in aqueous solutions above the boiling point of water, under high pressure and temperature in a sealed vessel.	High purity, controlled morphology, environmental friendliness.	High pressure, long synthesis time, requires specialized equipment.
Solvothermal Method	Similar to hydrothermal but uses organic solvents; reactions occur in a sealed vessel under high pressure and temperature.	Controlled particle shape and size, can produce unique morphologies.	Requires organic solvents, longer process times, high pressure.
Solid-State Reaction	Mixing solid reactants (zinc oxide and dopant compounds) and heating them at high temperatures to induce	Simple, cost-effective, suitable for large-scale production.	High temperatures required, potential for inhomogeneous doping, longer reaction times.

	diffusion and reaction.		
Physical Vapor Deposition	Physical processes (e.g., sputtering, evaporation) to deposit thin films of materials onto substrates in a vacuum environment.	High-purity films, good control over thickness and composition, suitable for thin films.	Expensive equipment, complex process, limited to thin films.
Chemical Vapor Deposition	Chemical reactions of volatile precursors in the gas phase to deposit solid material onto substrates, forming thin films or nanostructures.	High-quality films, precise doping control, scalable.	High temperatures, complex process, hazardous precursor gases.
Electrodeposition	Electrochemical process where zinc and dopant ions are reduced from a solution and deposited onto a conductive substrate by applying an electric current.	Low cost, scalable, good control over thickness and morphology, operates at low temperatures.	Limited to conductive substrates, uniformity depends on current distribution, possible hydrogen evolution.
Combustion Synthesis	Exothermic redox reactions between fuel and oxidizer precursors rapidly produce high temperatures, leading to the formation of doped ZnO nanoparticles.	Rapid, energy-efficient, simple setup, can produce high-purity products.	Less control over particle size and morphology, potential safety hazards due to high temperatures.

Nanotechnology in Skin Cancer Management

Polymeric micelles for skin cancer

In recent years, polymeric micelles have gained significant attention as advanced drug carriers for nanoscale drug delivery systems. Since many skin diseases can be effectively treated with topical medications, the ability of drugs to penetrate the skin barrier plays a crucial role in their therapeutic efficacy. While polymeric micelles outperform conventional topical formulations such as creams, ointments, and gels in delivering drugs through the skin, their clinical effectiveness remains limited due to insufficient drug permeation into targeted skin layers. However, these nanocarriers offer several advantages, including enhanced solubilization of drugs within the skin, improved deposition of hydrophobic drugs in the stratum corneum, and targeted delivery to hair follicles and keratinocytes within the epidermis. Additionally, polymeric micelles enable sustained and controlled drug release, making them a promising approach for dermatological applications. Although the skin barrier poses a challenge, conditions such as acne, psoriasis, and burns often involve alterations in skin structure, potentially enhancing the ability of polymeric micelles to facilitate targeted drug delivery [65].

Hydrogels

Hydrogels are hydrophilic polymeric networks with a three-dimensional (3D) structure capable of retaining substantial amounts of water. They can be synthesized using a variety of natural or biocompatible synthetic polymers, making them highly versatile in biomedical applications. Their unique attributes including high water content, adjustable mechanical properties, ease of fabrication, and controlled swelling and curing behaviors have made them widely applicable in drug delivery systems, tissue engineering, and wound healing over recent decades. In cancer therapy, particularly for melanoma skin tumors, hydrogel-based drug delivery formulations offer significant advantages over traditional treatment methods [66]. These systems facilitate sustained and controlled drug release, thereby enhancing therapeutic efficacy while minimizing off-target effects. Unlike traditional chemotherapy, hydrogel-based drug formulations offer several advantages that help minimize harmful side effects. By prolonging the drug's half-life, ensuring targeted delivery, and lowering systemic toxicity, hydrogels provide a more controlled and localized treatment approach [67]. These benefits make them a promising tool for precision medicine, as they can integrate both chemotherapy and gene therapy to enhance therapeutic effectiveness. Recent advancements in hydrogel technology have further improved their functionality by incorporating stimuli-responsive mechanisms. These innovations allow drug release to be activated by specific triggers such as changes in pH, temperature fluctuations, or enzymatic activity within the tumor microenvironment. This targeted delivery system increases drug concentration at the tumor site while reducing unnecessary exposure to healthy tissues, improving both efficacy and safety in cancer treatment [68].

Researchers have developed an innovative nanohybrid hydrogel by functionalizing chitosan with L-histidine (HIS) and incorporating zinc oxide nanoparticles (ZnO NPs) to improve the delivery of polyphenol-based therapeutics, such as naringenin (NRG), quercetin (QE), and curcumin (CUR). The optimized formulation demonstrated excellent drug-loading capacities, with efficiencies reaching 90.55% for NRG, 92.84% for QE, and 89.89% for CUR. The structural stability of the

hydrogel and its ability to provide controlled, sustained drug release were reinforced by the HIS–chitosan conjugation. This design enables prolonged drug administration, particularly under acidic conditions (pH 5), making it a promising platform for targeted therapeutic applications. Compared to free polyphenols, the nanohybrid hydrogel exhibited a remarkable 15- to 30-fold increase in cytotoxicity against human skin carcinoma (A431) cells, demonstrating its potential as an effective anticancer drug delivery system [69].

Recent studies

Despite the effectiveness of surgery and radiation therapy, skin cancer is also managed through immunotherapy, targeted therapy, and chemotherapy to eliminate as many cancer cells as possible. However, conventional chemotherapy suffers from a lack of tumor-specific targeting, resulting in inefficient drug uptake by tumors and widespread distribution throughout the body, leading to severe side effects. Additionally, many chemotherapeutic agents exhibit a poor half-life, low solubility, limited permeability, and inadequate stability under physiological conditions, which diminishes their therapeutic efficacy. For non-metastatic skin cancer where the disease has not spread to distant organs such as the brain, lungs, liver, or bones direct topical application of therapeutic agents at the tumor site offers a promising alternative [73-74]. This localized approach minimizes systemic toxicity and significantly reduces treatment costs. However, effective drug penetration into the skin tumor is hindered by the outermost barrier of the skin, the stratum corneum. To address these challenges, nanotechnology has emerged as a viable strategy to enhance drug delivery and improve therapeutic outcomes in skin cancer treatment. Among various nanomaterials explored for skin cancer therapy, nanoparticles (NPs) have garnered significant attention due to their unique advantages. These include passive tumor targeting via the enhanced permeability and retention (EPR) effect, the ability to evade the reticuloendothelial system (RES), and enhanced skin permeability [75].

Table 2: Zno Nanoparticles with recent studies in cell line [88]

Nano particles	Size of Particles	Cell Line Cytotoxicity Analysis
Zno nanoparticles	154.41 – 172.89 nm	Human epidermoid carcinoma cell line (A431)/ Human keratinocyte cell line (HaCaT)
Zno nanoparticles	10 – 20 nm	Human melanoma cell line (A375)
Zno nanoparticles	50 nm	Human epidermoid carcinoma cell line (A431)

One particularly promising class of nanoparticles is zinc oxide (ZnO NPs), which exhibit a dose-dependent response in inducing melanoma cell death and reactive oxygen species (ROS) generation. Studies have demonstrated that ZnO NPs modulate cell viability, apoptosis, and mRNA expression of apoptotic genes in cancer cells such as HepG2 (liver cancer) and MCF-7 (breast cancer) in a dose-dependent manner. For instance, in HepG2 cells treated with a low concentration of 25 µg/ml ZnO NPs, cell viability, as assessed through the MTT assay, dropped to below 10%, exhibiting a dose-dependent decline [76]. At higher concentrations, the process of apoptosis accelerates more rapidly. To assess the expression of key apoptotic markers, researchers conducted quantitative real-time polymerase chain reaction (PCR) analysis to examine mRNA levels of genes such as p53, Bax-2, bcl-2, and caspase-3. The findings showed that treated cells had a 1.9-fold increase in p53 mRNA levels, while the expression of bcl-2, an anti-apoptotic gene, decreased by 2.5-fold. Additionally, pro-apoptotic Bax mRNA levels were reduced by 2.7-fold, whereas caspase-3 expression increased by 1.8-fold, highlighting its involvement in apoptosis regulation. The activation of caspases begins when the mitochondrial membrane is disrupted, leading to the release of soluble proteins from the intermembrane space into the cytosol, further promoting cell death. ZnO nanoparticles (ZnO NPs) possess electrostatic properties that change with pH variations, affecting their surface charge. This characteristic makes them highly adaptable for conjugation with various therapeutic drugs, enhancing their potential for targeted treatment applications. In addition to serving as photodynamic agents, ZnO NPs generate high levels of ROS, which further induce apoptotic cell death. Metalloproteins have demonstrated anticancer properties, as their application has been found to reduce cell viability. Asparaginase-loaded ZnO NPs have shown excellent selectivity, efficacy, and stability as an anticancer agent. Moreover, chemotherapeutic drugs like paclitaxel and daunorubicin, when co-administered with ZnO NPs, exhibit reduced toxicity while maintaining their therapeutic potential [77-79]. The oxidative stress induced by well-crystallized ZnO NPs was assessed in Cloudman S91 melanoma cells, where hexagonal ZnO NPs (average size: 10 nm) effectively triggered ROS production and apoptosis in a dose-dependent manner [70]. Additionally, silver-doped ZnO NPs (Ag-ZnO NPs) have demonstrated potent anticancer activity against skin cancer while offering protective effects against harmful UV radiation [71]. Furthermore, gold-doped ZnO NPs (Au-ZnO NPs) have exhibited cytotoxic and anticancer properties in human melanoma (A375) and epidermoid carcinoma (A431) cells, as assessed by MTT assay following established protocols [72].

Conclusion

In this review, we have provided an in-depth analysis of doped ZnO nanoparticles and their potential role in the treatment of skin cancer. Their distinctive physicochemical properties, including enhanced photocatalytic activity, improved biocompatibility, and targeted therapeutic capabilities, highlight their promise for advancing skin cancer therapy. However, further research is essential to refine their formulations, assess long-term safety, and validate their clinical efficacy. Addressing these challenges could pave the way for the development of innovative and effective skin cancer treatments utilizing doped ZnO nanoparticles.

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