



A Nano-zinc Oxide-based Drug Delivery System and its Biomedical Applications

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Abstract

Zinc Oxide Nanomaterials (ZnO-NMs) are significant nanomaterials utilized in biological applications. Biopolymers have been widely employed in biomedicine due to their various benefits. ZnO nanoparticles coated with biopolymers have exhibited considerable promise in the medical domain. Over the last two decades, ZnO-NM has demonstrated remarkable luminous capabilities, and their affordability, minimal toxicity, and biological compatibility have positioned these nanomaterials as prime prospects for bioimaging applications. Identifying other advantageous characteristics, including the capacity to generate harmful Reactive Oxygen Species, elevated catalytic effectiveness, robust adsorption capacity, and an elevated isoelectric point, further establishes them as attractive nanomaterials for medicinal and diagnostic purposes. This document reviews current advancements in applying ZnO-NM for drug delivery and theranostics in various illnesses, including bacterial infections and cancer. The adaptation enhances the suitability of ZnO-NM by utilizing a biopolymer as a sealing driver, possibly augmenting efficacy in Drug Delivery (DD) and biomedical purposes. ZnO-NM, covered with biopolymers, has extensive applications in biomedicine, including drug delivery, biological imaging, and therapeutic interventions for cancer, microbiological diseases, and diabetes. Moreover, enhancements to ZnO-NM for pharmaceutical delivery frequently involve initiatives to augment biocompatibility, facilitate focused DD, and enhance uptake while mitigating side effects. The alterations improve the stabilization of nanomaterials and facilitate the connection of specific protein molecules for focused delivery and efficacy against diabetics and microbe illnesses.

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Introduction

In recent years, due to their extensive uses in many disciplines, especially medical research, biomedical substances in nanoparticle form, measuring 1 to 100 nm, have gained prominence in research (Mabrouk et al., 2021). The results suggest that a practical approach for producing diverse biological materials lies within the emerging domain of nanoscience and nanotechnologies. The scientific world has recognized nanoparticles due to their exceptional variability in size, shape, structure, and surface characteristics. Recent breakthroughs in nanotechnology and medical studies have concentrated on constructing nanomaterial technologies for biomedical applications. The capacity to selectively target specific bodily cells and administer payloads enhances the precision and efficacy of nanomaterials-based biomedical products. Utilizing biological concepts in medical treatment is called "biomedicine," which emphasizes integrating biomedical studies with technological advances to enhance the understanding of infections, formulate therapies, and elevate the quality of life (Javaid et al., 2023). Various nanostructures have been produced, including metalloids, metallic oxides, and non-metal carbon nanostructures. Their utilization in the biomedical sector is facilitated by extensive surface region, diminutive region, and elevated reaction (Uyan, 2022).

Zinc Oxide Nanomaterials (ZnO-NMs) belong to the most recognized metal oxide nanomaterials (Wojnarowicz et al., 2020). ZnO-NMs can be utilized across various industries due to diverse chemical and physical characteristics, like higher chemical vulnerability, elevated electrochemical connecting aspect, extensive absorbed radiation range, significant photostability, and simple morphological alteration. ZnO-NMs are a substantial constituent of several materials and products. Applications include medicines, ceramics, power sources, and environmental items, such as air filtration and water treatment technology (Asif & Zhang, 2021). ZnO-NMs are an excellent choice for biomedical and sustainability due to their durability and biological compatibility. It can function as an energy substance, effectively storing, converting, or creating energy for many applications, including medication administration, medical imaging, biological detection, and exhibiting antibacterial, antioxidant, cancer-preventing, and anti-inflammatory characteristics (Bigham et al., 2024).

Various synthesis strategies, including physical, chemical, and biological methods, can be employed to create ZnO-NMs. For several years, applying organic dye molecules has facilitated the detection and monitoring of diverse chemicals, such as medicines, amino acids, nucleic acids, and materials, both intracellularly and extracellularly (Ghalkhani et al., 2022). They are utilized to investigate biochemical processes (enzymatic synthesizing, immunological response, etc.) or to diagnose certain disorders. Its application in bio-imaging has significantly diminished with the emergence of nanoparticles. Nanomaterials demonstrate excellent stability against photochemical deterioration, possess broad excitation wavelength categories, and display narrow, symmetrical emission spectra, with color variations contingent upon particle size (known as the quantum size impact) (Ansari et al., 2022; Salih & Nangir, 2024).

ZnO-NMs have been produced in various nanospheres, rods, tubes, rings, belts, and flowers. ZnO-NMs provide a diverse chemical makeup of the surface that is readily adjusted to inhibit aggregation, enhance colloidal security, or acquire novel features for Drug Delivery Structures (DDS) (Batoool et al., 2021). The application of DDS in nanotechnology presents critical benefits over conventional pharmaceuticals: (i) enhancing the solubility of medications that are poorly absorbed by cells, thereby improving their accessibility; (ii) preventing the breakdown of particular medications that are unsteady at biological or digestive pH; and (iii) minimizing toxicity and adverse effects by employing targets that augment treatment selection (Al Ragib et al., 2022). Given their capability to generate reactive oxygen species, function as drug delivery systems, and exhibit luminescent features, they can discuss theranostic nanotechnologies in which ZnO-NMs serve as imaging and therapeutic agents.

This article emphasizes the notable progress regarding the functionality of ZnO-NMs and surface-changed ZnO-NMs, which exhibited promising healthcare applications due to their antibacterial, drug-delivery, biological imaging, and antidiabetic capabilities.

Synthesis of ZnO-NMs

The regulation of the dimensions, form, framework, content, and cleanliness of their components enables the production of nanostructures to exhibit desirable attributes that are adjusted to meet specific needs. Two primary methodologies are often utilized in synthesizing nanotechnologies: top-down and bottom-up techniques (Abid et al., 2022). A significant quantity of components was mechanically diminished to nanoscale using the approach. In contrast, the bottom-up model employs biological procedures to construct nanostructures from atoms or atoms. ZnO-NMs have been produced in diverse introductions, shapes, sizes, and forms, primarily utilizing two methodologies known as conventional and nontraditional procedures (Batra et al., 2022). ZnO-NMs are manufactured utilizing non-conventional technologies, namely the microfluidic reactor approach. ZnO-NMs are manufactured using traditional physical, chemical, and biological methods.

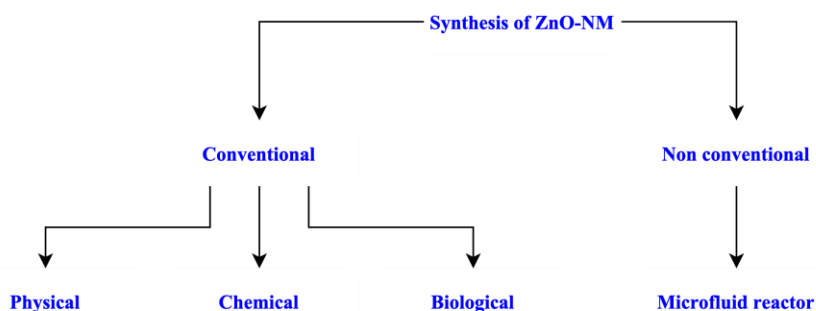


Figure 1. Synthesis techniques of ZnO-NM

Figure 1 depicts the various techniques employed to produce ZnO-NMs. Chemical approaches are predominantly used for producing ZnO-NMs due to their durability and ability to deliver high-quality results (Islam et al., 2022). Physical methods are the least utilized among these strategies, while biological methods rank second most prevalent. The utilization of physical forces such as heat, electromagnetic energy, and electrical discharge is called physical synthesizing.

Physical methods possess drawbacks such as elevated energy consumption, mechanical stress, and a broad particle size dispersion despite being more rapid and necessitating fewer chemical agents. ZnO-NMs are produced using a physical method encompassing ball milling, sparking, laser-induced ion injection, etc. This method is the predominant technique for synthesizing ZnO-NMs. The benefits of chemical approaches include cheap cost, excellent surface adaptability, ease of modification, high yields, size oversight, thermal resistance, and reduced dispersity (Ahmed et al., 2022).

In the synthesis process, the substances utilized are flammable and non-biodegradable. ZnO-NMs are manufactured using these methods, explicitly utilizing techniques such as aerosol, sol-gel, precipitation, vapor condensate, heat treatment, rainfall, and solve-heat methods processes. Due to the absence of toxic chemicals in manufacturing ZnO-NMs, biosynthesis is regarded as ecologically friendly. ZnO-NMs are efficiently manufactured using biological methods utilizing natural settling down, restricting, and decreasing agents such as nutrients, flavonoids, sugar, and amino acids.

Alternative solutions that are more cost-effective and ecologically sustainable are feasible. Applications in biology gain advantages from biologically created nanoparticles due to their typically lower cytotoxicity. ZnO-NMs are produced biogenically using plant-mediated and microbe-mediated methods. The exterior chemistry, distribution of sizes, morphology, and responsiveness of ZnO-NMs all affect function in biology. The synthesis of ZnO-NMs with controlled architectures that exhibit uniformity in size, shape, and activity is essential for many uses in biology (Zubair & Akhtar, 2020).

The biological manufacturing of ZnO-NMs has garnered increased interest due to its sustainability, cost-effectiveness, and environmental friendliness. ZnO-NMs are manufactured using natural biological materials, including microorganisms like algae, fungi, microbes, and plant components. Synthesis is one of the two prevalent biological approaches for producing ZnO-NMs. They serve as safer alternatives to toxic compounds. Figure 2 illustrates the fundamental procedures for making a biological extraction. A living substrate from microorganisms (pathogens, fungus, algae) or vegetation (veggies and flowers) amalgamated with compounds. ZnO-NMs are synthesized by heating the residual mixture after the reaction evaporation in a microwave (Mostafa et al., 2020).

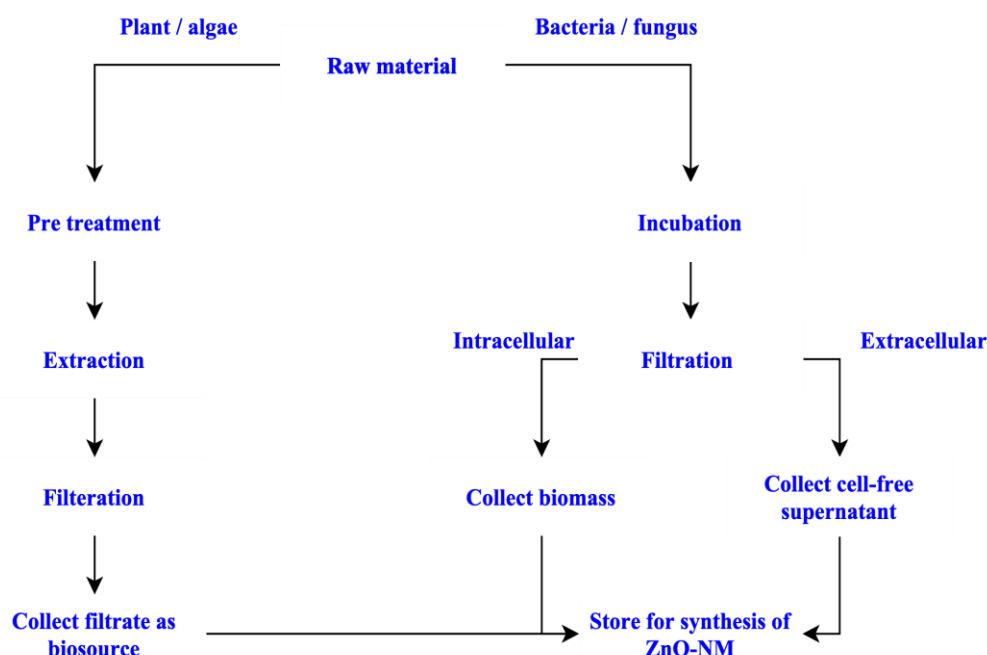


Figure 2. Biosynthesis of ZnO-NM

Methods

The predominant and extensively employed method for synthesizing ZnO-NMs involves a chemical procedure utilizing organic and inorganic substances as reduction drivers. The sol-gel, hydrothermal, and solve-heat procedures constitute a substantial segment of the established and efficient synthesis techniques employed to generate stable ZnO-NMs.

Sol-Gel Method

Sol-gel technologies have become more prominent in manufacturing metal oxide nanomaterials, particularly in producing exceptional ZnO-NMs. Creating sol via the precursor and its subsequent conversion into a gel underpins the procedure. Upon drying the gel, the solution is extracted from the matrix, allowing it to maintain

its gel form. The unique characteristics of drying methods for dried gel encompass cooling, thermal treatment, and supersonic drying, resulting in the transformation of the gel, becoming cryogel, xerogel, and aerogel, accordingly. Figure 3 illustrates the many steps of the sol-gel method. The synthesis of higher-effectiveness ZnO-NMs is achievable due to the technique's advantages, that operates effectively around 100 and 1200°C.

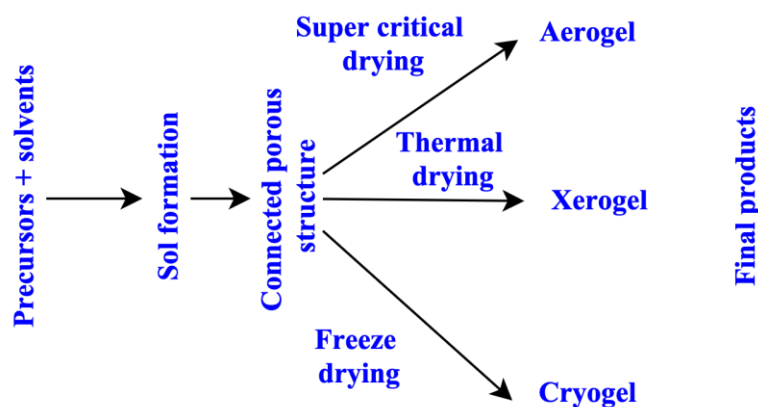


Figure 3. Sol-gel process for ZnO-NMs

ZnO-NMs were made using water from distillation as the solvents, alcohol, and zinc acetate dihydrate as their precursor. The zinc solution was combined with alcohol at the surrounding heat (Duško et al., 2021). A gel is generated by sustaining the solutions. NaOH is utilized to mix the mixture, which is agitated for 1 hour, resulting in the subsequent formation of white precipitates.

Before calcination, drops are dehydrated on a plate. The produced ZnO-NMs were examined by UV-visible spectroscopy, X-Ray Diffraction (XRD), and Scanning Electron Microscopy (SEM). The nonmaterial dimensions were determined to be around 18 and 23 nm in the SEM study, 80 and 85 nm in the examination, and around 240 nm in the survey.

Saka et al. utilized hexahydrate of zinc nitrate, isopropyl solution, and liquid from distillation as a medium to produce nanosized ZnO-NMs (Saka et al., 2024). Nitric acid maintained the pH scale, and glycerine was mixed in a 1:5 ratio. The composite material was stirred, resulting in a sol. Upon heating, the resultant sol yielded a solution. The solution underwent calcination at various degrees. The size range of ZnO-NMs ranged from 60 to 120 nm, and an increase in the calcining temperature resulted in particulate aggregation into a composite material measuring 250 to 500 nm.

Hydrothermal Method

The hydrothermal method utilizes an aqueous mixture, often performed at elevated temperatures and tensions within a sealed reaction container Figure 4. This approach has demonstrated a groundbreaking potential for manufacturing metal oxide nanomaterials. The material in combination is subjected to a temperature ranging from 110 to 280 °C in a microwave during the hydro-heat process's initial phase, which entails mixing the combination for a few minutes to yield the end result in a sterilized container. The mixture is dried out in an oven according to its constitution. This approach yields exceedingly pure metal oxide nanoparticles. The principal benefit of the hydrothermal approach is its ability to generate significant, very pure ZnO-NMs. This procedure effectively regulates the element dimension and morphology of the substance to be produced.

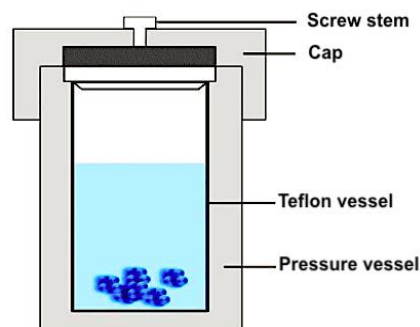


Figure 4. Hydrothermal approach for Zn-NMs

Rajamanickam et al., synthesized ZnO-NMs using zinc acetate and alcohol in a 1:4 proportion (Rajamanickam et al., 2020). The mixture was agitated continuously for 1 hour. Sodium hydroxide is incrementally included and agitated to regulate the pH. ZnO-NMs were eventually acquired. The synthesized ZnO nanoparticles are analyzed using XRD, Field Emission SEM (FESEM), and Energy-Dispersive Spectroscopy (EDS). The analysis indicated that the ZnO-NMs measured 54 nm in size. FESEM examination confirmed a nearly spherical shape with a mean dimension of 110 nm. The assessment confirmed that the ZnO-NMs exhibited a prominent maximum density for zinc, with no detectable elemental traces.

Chandana et al., utilized a zinc nitrate hexahydrate and a water-based ethanol solution to synthesize wurtzite hexagonal-structured ZnO-NMs (Chandana et al., 2023). After that, the zinc solution was solubilized in an alcoholic ethanol solution containing 1 M NaOH. A centrifugal method was utilized to isolate the precipitates. The precipitation of ZnO-NMs was heated. The XRD examination indicates that the nanomaterials measure 34 nm in dimension. SEM examination reveals the homogeneous, hexagon-like shape of ZnO-NMs.

Solvothermal Process

The hydro-heat technique and the solve-heat approach are analogous to a degree. In industrial and biomedical applications, metal oxide nanomaterials exhibiting characteristics are precisely manipulated in size and crystal arrangement via the solvothermal method, commonly employed for their synthesis in water or solid solutions.

The nanomaterials are created using the solvothermal process, which involves the production of metal oxide nanomaterials at hot temperatures (150-1200°C) and high forces. Approximately half as many publications are written on manufacturing as synthesis. Izgis et al. produced ZnO-NMs by combining zinc acetate dihydrate with ethanol (Izgis et al., 2022). The mixture was maintained in a 120 ml Teflon sterilizer. The whole combination was subjected to centrifugation. Shortly after the extraction process, the white comes had been heated in a microwave and heated in a heater. The synthesized ZnO nanoparticles were examined using SEM, UV spectroscopy, EDS, and XRD techniques. The resultant ZnO-NMs exhibited a nearly spherical morphology and a hexagonal wurtzite configuration. XRD, SEM, and EDS investigations indicated NP diameters of 0.17 nm, roughly 20–45 nm, and the absence of contaminants in ZnO-NMs.

Drug Delivery Applications

“Targeted drug treatment” is a therapeutic modality wherein a patient is administered a pharmaceutical precisely engineered to target sick cells, preserving healthy cells from damage selectively. Nanoparticles enhance targeted medicine delivery to malignant locations. The advancement of nanoparticles for targeted medication delivery presents promising new options for identifying and treating critical illnesses. The nano DDS presents significant promise for targeting agonists, improving surface curves, pharmaceutical kinetics

and metabolism, and altering the dissolution of hydrophilic medicines because of its diminutive size and extensive extent of surface. The biomedical transport system must employ three tactics to improve medication release effectiveness. They provide targeted distribution, enhance dissolution, and modulate the escape of active constituents (Khyade & Wanve, 2018). The biomedical applications of ZnO-NMs are represented in Figure 5.

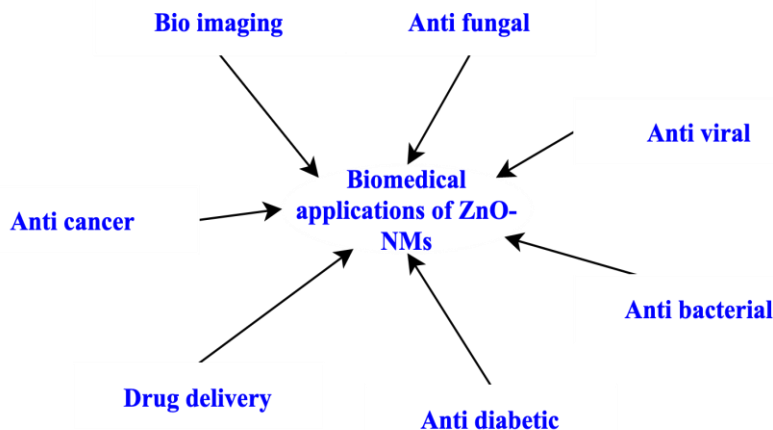


Figure 5. Biomedical applications of ZnO-NMs

ZnO-NMs are among the most promising metal oxide nanoparticles for specific drug delivery due to their particular visual and semiconductor characteristics, simple synthesis, higher drug capacity, versatile model, and the ability for focused drug distribution. Due to its flexibility, improved biological compatibility, and capacity for dose-controlled release of drugs, ZnO-NMs have gained significant prominence in drug delivery applications. They consist of both synthetic and organic polymers. The pH dependency or acidity-triggered biological activity of ZnO-NMs is a crucial advantage in drug development and shipment, as it significantly enhances cancer targeting and therapeutic efficacy.

Drug delivery methods can use the beneficial diagnosis and imaging capabilities provided by the luminescent characteristics of ZnO-NMs. Porous-shaped ZnO-NMs have been successfully utilized for targeted medication delivery. Due to its enduring antimicrobial and antitumor attributes, diminished hazardous impacts, and ZnO-NMs are extensively used. When ZnO-NMs are surface-changed for drug administration, the objectives often include improving safety while optimizing biological compatibility, specific drug delivery, and cellular penetration. The predominant techniques include coating the surface of ZnO-NMs with biologically friendly chemicals, such as detergents or bio-polymers. These changes enhance the stabilization of nanomaterials and facilitate the binding of specific amino acids for directed administration.

Anticancer DDS

Cancer is a dangerous disease that arises when cellular proliferation occurs improperly and uncontrolled. It frequently culminates in mortality following the destruction of normal cells. Cancer therapies often encompass surgical intervention, immunotherapy, chemotherapy, radiotherapy, and targeted pharmacological treatment. While these medications yield remarkable results, they have undesirable adverse reactions—chemotherapy functions by inhibiting or stopping the rapid proliferation and division of neoplastic cells.

Besides eradicating rapidly proliferating tumor cells, chemotherapy impedes or halts normal tissues' rapid growth and division. Radiation treatment effectively eradicates tumor cells or inhibits their proliferation, although it adversely affects adjacent healthy cells. Damage to normal cells results in adverse outcomes.

Immunotherapy eliminates aberrant cells through the body's immune response, inhibiting or substantially decelerating the proliferation of tumor-like cells.

Immunotherapy induces the body's defenses to target healthy cells. Targeted pharmacological treatment has been employed to resolve the concerns above. Targeted medications, which use drugs designed to attack cancer cells while sparing normal cells selectively, have the chance to transform cancer treatment. The systemic adverse effects of traditional medical interventions are mitigated, as nanoparticles can deliver normally insoluble drugs more efficiently to proximal and distal tumor sites. ZnO-NMs can infiltrate malignant cells and provide anticancer therapeutics.

Based on a cytotoxic investigation, drug-loaded ZnO-NMs showed superior anticancer activity compared to bare ZnO-NMs and doxorubicin. The cytotoxic efficacy of the antitumor agent doxorubicin could be enhanced by its incorporation with ZnO-NMs due to the beneficial interaction stemming from their joint anticancer properties. ZnO-NMs are detrimental to tumors through many mechanisms, including the induction of oxidative damage inside these malignant cells. ZnO-NMs disrupt mitochondria and promote oxidative damage in malignant cells. ZnO-NMs penetrate tumor cells, affecting the mitochondria and resulting in the death of the tumor cell. Alteration to the ZnO surface aims to regulate the absorption of medicinal chemicals to enhance efficacy against tumor cells while reducing adverse reactions.

The study produced an elongated plate-like form of monodispersed eggs albumin-doped ZnO (Ea-ZnO), which exhibited notable efficacy in treating breast cancer lineages. The assay demonstrates that Ea-ZnO nanoparticles exhibit considerable toxicity and reduced life span compared to cells. Reactive Oxygen Species (ROS) helps apoptosis in cancer tissues, which effectively regulates the development of pathways. Correlating cytotoxicity and decomposition with cell demise can selectively inhibit the encoding of the genes.

Perforated ZnO-NMs (PZnO-NMs) exhibiting a structure composed of hexagonal wurtzite were produced. Cisplatin was utilized for encapsulation with PZnO-NMs. A laboratory experiment has shown that the absorption of cisplatin by ZnO-NMs leads to a slight increase in pH and is not associated with any detrimental effects during the release of medications from PZnO-NMs. 51% of the cisplatin was effectively included within PZnO-NMs. On one day, the maximum emission was 9% at pH 5.8. The focused distribution of enclosed PZnO-NMs to tumors and the little release of platinum to malignant cells reduces the dosage periods necessary for effectively eliminating malignancies.

Hexagonal-shaped ZnO-NMs were synthesized utilizing an aloe barbadensis extract of the leaf. The drug unloading capability was assessed by the administration of gemcitabine (GEM) and docetaxel (DOX). Polyethylene Glycerol (PEG) was employed to modify ZnO nanoparticles. In comparison to GEM, DOX demonstrated a superior capacity for loading drugs.

The study produced methotrexate-conjugated ZnO-NMs (MTX-ZnO-NMs), demonstrating significant therapeutic efficacy using an in cancer cell. The findings released tests that indicated the efficacy of MTX-ZnO-NMs in inhibiting the proliferation of A549 cells. Caspases-9, -8, and -3 were markedly triggered by MTX-ZnO-NMs at 120-850 ng/mL concentrations and MTX alone at 1-7 $\mu\text{g/mL}$ concentrations. MTX can cause apoptosis through caspase-based and not-based mechanisms. ZnO nanoparticles were utilized as nanocarriers to transport MTX to the tumor efficiently.

The study created ZnO-NM, which exhibited resistance to the EAC cancer cell. The synthesized ZnO-NM included ZnO-NMs, ZnO-NMs/DOX, ZnO-NMs/FA (Folic Acids), and ZnO-NMs/DOX/FA. The treatment of cancer was assessed utilizing the test. The GraphPad program was used to ascertain the EAC

tumor line's 50% inhibition concentration (IC50) values. ZnO-NMs conjugated with doxorubicin, folic acid, doxorubicin, and folic acid were utilized in the in vivo investigation involving mice subjected to an EAC test. Following the ZnO-NM therapy, there was a minor reduction in the overall count of treatable tumor cells. However, a substantial rise in the total quantity of treatable tumor cells was observed. ZnO-NM/DOX/FA markedly mitigated hepatic and kidney damage induced by the implantation of EAC in mice subjected to difficulty, and it substantially reduced.

Conclusion

This bibliographic evaluation illustrates that zinc oxide nanoparticles exhibit distinct properties: (i) glowing; (ii) dissolution of zinc ions in aqueous environments, particularly under acidic circumstances; (iii) the production of reactive oxygen species, primarily upon UV irradiation; (iv) adaptable surface a connection; and (v) a straightforward and cost-effective synthesis method that enables precise control over particle size and morphology. These features render the nanomaterial exceptionally adaptable, whether utilized independently or with additional elements. ZnO-NMs are adaptable and are customized for specific biological applications such as medication administration, images, and prevention of infections. Their diminutive size enables them to selectively target particular cells within the body, enhancing the precision and efficacy of therapies. Chemical and biogenic methods have proven helpful in producing high-quality ZnO-NMs. Unique coatings composed of synthetic or natural biopolymer components are employed to change the area of ZnO-NMs. ZnO-NMs and biopolymer-modified ZnO-NMs possess medicinal uses, such as drug delivery, biological imaging, and therapeutic interventions for tumors, microbial illness, and diabetes. This result indicates that ZnO-NMs are utilized to maximize efficacy in treatment. Changing the exteriors of ZnO-NMs with biopolymers has yielded intriguing fresh perspectives.

A consistent methodology (including concentrations and durations of activity) is necessary to acquire comprehensive knowledge regarding the impact of nanomaterials, hence hindering their clinical application. Considering the evidence, the researchers contend that this is just its inception, ZnO-based nanotechnology will not only attain medical significance but facilitate the introduction of new innovative theranostic uses.

Author Contributions

All Authors contributed equally.

Conflict of Interest

The authors declared that no conflict of interest.

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