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Review Article

Therapeutic Potential of ZnO-Nanoparticles Synthesized Using *Portulaca oleracea* in Cancer Treatment: A Comprehensive Narrative Review

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ABSTRACT

Cancer remains a leading global health challenge, with conventional therapies often hindered by severe side effects and the emergence of resistance. Nanotechnology presents innovative approaches for targeted cancer treatment, with zinc oxide nanoparticles (ZnO-NPs) gaining attention for their ability to generate reactive oxygen species (ROS) and induce apoptosis. This review explores the green synthesis of ZnO-NPs utilizing the bioactive plant *Portulaca oleracea* (purslane), emphasizing its eco-friendly and biocompatible nature. This comprehensive narrative aims to investigate the synthesis, characterization, and mechanisms of action of ZnO-NPs synthesized using *P. oleracea*, synthesis methodologies, physicochemical properties, anticancer mechanisms, and potential applications across multiple cancer types, including breast, lung, colorectal, prostate, and ovarian cancers. Additionally, the review discusses the challenges associated with biocompatibility, scalability, and clinical applications while highlighting potential pathways for further investigation.

ZnO-NPs synthesized using *P. oleracea* exhibit notable anticancer efficacy due to enhanced ROS generation and targeted apoptosis. Preliminary studies highlight their potential in delivering lower-toxicity alternatives, compared to conventional treatments. Despite promising results, scalability, clinical application, and long-term biocompatibility remain significant challenges. ZnO-NPs synthesized via green methods represent a transformative approach to cancer treatment. However, further research addressing biocompatibility, regulatory hurdles, and large-scale production is essential to advance their clinical application.

1. Introduction

Cancer is a complex group of diseases characterized by uncontrolled cell growth, invasion into surrounding tissues, and the potential to spread to other parts of the body (metastasis). It arises due to genetic mutations, environmental factors, and lifestyle choices, leading to disruptions in normal cellular processes, such as growth regulation, DNA repair, and apoptosis[1,2]. Cancer remains one of the leading causes of death worldwide amid an ever-increasing need for more innovative and effective forms of therapy. Traditional chemotherapy, radiation, and surgical treatment are useful but usually involve serious side effects and limitations owing to drug resistance and nonspecific impacts on normal tissues. Within the last 10 years, nanotechnology has arisen as a potentially powerful strategy toward overcoming such issues, opening new perspectives in the design of targeted therapies against

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cancer[1]. Due to their specific physicochemical properties, including the capability to induce reactive oxygen species (ROS) generation, apoptosis, and to act as carrier systems for therapeutic agents, zinc oxide nanoparticles (ZnO-NPs) are receiving growing interest in oncology[2]. Various green synthesis techniques using botanical extracts for the preparation of biocompatible and environmentally friendly nanoparticles have considerably pushed the use of ZnO nanoparticles in oncological therapies[3]. Purslane (*Portulaca oleracea*) is a succulent plant that has been used in folk medicine for centuries. It contains flavonoids, alkaloids, vitamins, and omega-3 fatty acids, which are responsible for its anti-inflammatory, antioxidant, and anticancer activities[4]. Thus, these compounds make *P. oleracea* an ideal candidate for the green synthesis of ZnO-NPs, as this may enhance their therapeutic efficacy and reduce toxicity. The focus of the narrative review will be to provide an overview of the therapeutic potential of ZnO-NPs synthesized using *P. oleracea* in treating cancer.

We will discuss in detail the synthesis process, characterization techniques, mechanisms of action, applications in several types of cancers, as well as the challenges and future perspectives associated with clinical use.

2. Synthesis and Characterization of ZnO-Nanoparticles

2.1. Green Synthesis Using Portulaca oleracea

Green synthesis of NPs is one of the fastest-growing areas of research due to increased interest in the use of nontoxic and biocompatible materials for biomedical applications[5]. Unlike traditional chemical synthesis methods of nanoparticles, which may require harmful reagents or severe reaction conditions, green synthesis involves the use of natural products as reducing/capping agents, offering minimal environmental impacts and providing improved biocompatibility to the synthesized nanoparticles[6]. *P. oleracea* is highly suitable for the green synthesis of ZnO nanoparticles, owing to its high concentration of bioactive compounds[7]. The synthesis generally involves the preparation of an aqueous extract from the plant by collecting, washing, drying, and grinding various parts of the plant. Then, the resultant powder undergoes aqueous extraction, which gives a solution rich in phytochemicals. When this botanical extract is added to a solution of zinc salts, such as zinc acetate or zinc nitrate, the active phytochemicals within *P. oleracea* reduce the zinc ions (Zn^{2+}) into zinc oxide (ZnO)[8]. This is catalyzed by functional groups, more so by hydroxyl and carboxyl groups, which may act as electron donors for the reduction process of the zinc ions into the synthesis of ZnO-NPs[9]. Control of the reaction conditions, considering pH, temperature, and the period for which the reaction takes place, is important for affecting the size, morphology, and stability of nanoparticles. In general, a high pH allows small nanoparticles to grow with a more homogeneous size distribution, while temperature might have an influence on both crystallinity and the rate of nanoparticle growth[10].

These all parameters need to be optimized in order to develop ZnO-NPs possessing desirable properties for therapeutic applications, such as uniform size, high surface area, and stability in the biological environment.

3. Characterization Techniques

Characterization of ZnO-NPs is a very important task to be performed, which assures that the nanoparticles have proper physical and chemical properties for the proposed therapeutic application. Thus, several advanced techniques have been employed to analyze the size, morphology, surface chemistry, and crystallinity of nanoparticles.

3.1. X-ray Diffraction (XRD)

The XRD technique is a tool that helps in the elucidation of the crystalline architecture and phase integrity of ZnO-NPs. The diffraction patterns obtained from XRD studies give information about the size of the crystallites, thereby confirming the formation of the wurtzite structure of ZnO characterized by its well-pronounced sharp peaks[11].

While SEM and TEM both provide different yet complementary roles in the characterization of nanoparticles, SEM is useful for providing high-resolution images showing the surface morphologies and dimensional distribution of the nanoparticles, thereby enabling research into the shape and texture of ZnO-NPs[12]. On the other hand, TEM allows an in-depth study of the internal structure of the nanoparticles, defining their dimensions at the atomic scale and confirming the nanoscale nature of the particles[13].

3.2. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR was done to identify the functional groups present on the surface of ZnO nanoparticles. This analysis is particularly useful for the confirmation of the presence of phytochemicals from *P. oleracea* on the surface of the NPs responsible for enhanced biocompatibility and therapeutic efficiency[14]. The FTIR spectrum usually presents peaks assignable to stretching vibrations of O-H, C=O, and C-H[15].

3.3. DLS

This technique measures the hydrodynamic diameter of nanoparticles in solution, providing information on size distribution and colloidal stability[16]. The low PDI evidences that there is a very uniform size in the nanoparticles, an important aspect for maintaining a consistent therapeutic efficiency.

3.4. Zeta Potential Analysis

Zeta potential essentially provides an estimate of the surface charge seen on nanoparticles, which plays a significant role in their stability and interaction with biological membranes. A very high negative or positive zeta

potential state that the nanoparticles remain stable in suspension and will hence show a lesser tendency to aggregate, increasing their feasibility for biomedical applications[17].

Proper application of these techniques of characterization will be vital in establishing if the ZnO-NPs synthesized using *P. oleracea* meet the necessary quality standards that will ensure successful oncological treatment. Correctly characterized nanoparticles are bound to give the expected biological results related to selective cytotoxicity and increased therapeutic efficiency[18].

4. Mechanisms of Action in Cancer Treatment

4.1. Induction of Apoptosis

One of the primary mechanisms by which ZnO-NPs exert their anti-cancer effects is through the induction of apoptosis, or programmed cell death. Apoptosis is a highly regulated process that allows the body to eliminate damaged or abnormal cells in a controlled manner, without causing inflammation or damage to surrounding tissues. ZnO-NPs induce apoptosis in cancer cells primarily by generating ROS[19]. ROS are chemically reactive molecules that can cause oxidative damage to cellular components, including lipids, proteins, and DNA[20]. Cancer cells, which often have elevated levels of ROS due to their high metabolic activity, are particularly vulnerable to further oxidative stress. The ROS generated by ZnO-NPs disrupt the mitochondrial membrane potential, leading to the release of cytochrome c from the mitochondria into the cytoplasm[21]. This event triggers the activation of caspases, a family of proteases that play a central role in the execution of apoptosis[22]. Activated caspases cleave key cellular proteins, leading to the characteristic morphological changes associated with apoptosis, such as cell shrinkage, chromatin condensation, and DNA fragmentation[23]. ZnO-NPs synthesized using *P. oleracea* may exhibit enhanced apoptotic effects due to the presence of bioactive compounds that can synergize with the nanoparticles[24]. Accordingly, flavonoids and alkaloids present in *P. oleracea* have been shown to modulate signaling pathways involved in oxidative stress and apoptosis, potentially amplifying the effects of ROS generated by ZnO-NPs[25].

4.2. Selective Cytotoxicity

Selective cytotoxicity is a critical feature of effective cancer therapies, as it allows for the targeted killing of cancer cells while minimizing damage to healthy cells[26]. ZnO-NPs exhibit selective cytotoxicity due to the unique metabolic characteristics of cancer cells (e.g., their reliance on glycolysis for energy [the Warburg effect], lower antioxidant capacity, and altered pH levels)[27]. The selective cytotoxicity of ZnO-NPs is primarily driven by their ability to generate ROS specifically within cancer cells[28]. The bioactive compounds in *P. oleracea* enhance this effect by increasing the oxidative stress experienced by cancer cells, leading to cell death[29]. In contrast, normal cells, which have higher antioxidant defenses and more stable metabolic environments, are less affected by the ROS generated by ZnO-NPs[30]. Studies have demonstrated that ZnO-NPs synthesized using *P. oleracea* can induce significant cytotoxicity in a variety of cancer cell lines, including breast, lung, and colorectal cancer cells, while exhibiting minimal toxicity to normal cells[31]. This selective targeting of cancer cells is particularly valuable in reducing the side effects associated with traditional chemotherapy, which often harms healthy tissues and leads to adverse outcomes, such as immunosuppression and organ damage[32].

4.3. Synergy with Chemotherapy

The combination of ZnO-NPs with conventional chemotherapy drugs represents a promising strategy for enhancing the efficacy of cancer treatment[33]. Chemotherapy drugs, while effective, often face challenges, such as poor solubility, limited bioavailability, and the development of drug resistance in cancer cells[34]. ZnO-NPs can address these challenges by acting as drug carriers, improving drug delivery, and sensitizing cancer cells to the effects of chemotherapy[35]. ZnO-NPs synthesized using *P. oleracea* can be conjugated with chemotherapeutic agents, creating a nanoparticle-drug complex that enhances drug stability and delivery to the tumor site[36]. Therefore, when combined with doxorubicin, a widely used chemotherapeutic agent, ZnO-NPs can increase drug uptake by cancer cells, leading to enhanced cytotoxicity[37]. The ROS generated by ZnO-NPs further sensitizes cancer cells to the chemotherapeutic agent, overcoming resistance mechanisms that often limit the effectiveness of chemotherapy[38]. In addition to improving drug delivery, ZnO-NPs can reduce the required dosage of chemotherapeutic agents, potentially lowering the risk of side effects[39]. This is particularly important in the treatment of aggressive cancers, where high doses of chemotherapy are often necessary but can lead to severe toxicity and reduced quality of life for patients[40].

5. Applications in Various Cancer Types

5.1. Breast Cancer

Breast cancer is the most common cancer among women worldwide and remains a leading cause of cancer-related deaths[41]. The heterogeneity of breast cancer, characterized by its various molecular subtypes, presents significant challenges for treatment. Triple-negative breast cancer (TNBC), in particular, is an aggressive subtype that lacks hormone receptors and HER2 expression, making it resistant to hormone therapy and HER2-targeted treatments[42]. ZnO-NPs synthesized using *P. oleracea* have shown promise in targeting TNBC and other breast cancer subtypes through ROS-mediated apoptosis and selective cytotoxicity[43]. Studies have demonstrated that these nanoparticles can effectively induce cell death in TNBC cell lines, reducing tumor growth in preclinical models[44].

The combination of ZnO-NPs with conventional chemotherapeutic agents, such as paclitaxel or doxorubicin, has further enhanced treatment efficacy, suggesting that these nanoparticles could play a critical role in overcoming drug resistance and improving outcomes for breast cancer patients[45]. Moreover, the anti-inflammatory and antioxidant properties of *P. oleracea* compounds may help mitigate some of the adverse effects of chemotherapy, such as inflammation and oxidative damage to healthy tissues[46]. This dual functionality makes ZnO-NPs synthesized with *P. oleracea* a promising candidate for more targeted and less toxic breast cancer therapies[47].

5.2. Lung Cancer

Lung cancer, particularly non-small cell lung cancer (NSCLC), is a major cause of cancer-related mortality worldwide[48]. NSCLC accounts for approximately 85% of all lung cancer cases and is often diagnosed at an advanced stage, limiting treatment options and reducing survival rates[49]. ZnO-NPs synthesized with *P. oleracea* offer a novel approach to lung cancer treatment by leveraging their ROS-generating capabilities to induce apoptosis in NSCLC cells[50]. These nanoparticles have been shown to disrupt mitochondrial function and increase oxidative stress in cancer cells, leading to cell death[51]. The use of *P. oleracea* in the synthesis process enhances the biocompatibility of ZnO-NPs, reducing the risk of adverse effects on normal lung tissue[52]. In addition to their cytotoxic effects, the anti-inflammatory properties of *P. oleracea* may help reduce the chronic inflammation associated with lung cancer progression[53]. By modulating inflammatory pathways and reducing the production of pro-inflammatory cytokines, ZnO-NPs synthesized with *P. oleracea* could improve patient outcomes and enhance the effectiveness of existing treatments, such as targeted therapy and immunotherapy[54].

5.3. Colorectal Cancer

Colorectal cancer is the third most common cancer globally and a leading cause of cancer-related mortality[55]. The treatment of colorectal cancer typically involves a combination of surgery, chemotherapy, and radiation; however, resistance to chemotherapy drugs, such as 5-fluorouracil (5-FU) remains a significant challenge[56]. ZnO-NPs synthesis using *P. oleracea* has demonstrated potential in enhancing the efficacy of colorectal cancer treatments by targeting cancer cells with high specificity and inducing apoptosis[57]. These NPs can increase the uptake of chemotherapeutic agents like 5-FU by cancer cells, overcoming drug resistance and improving treatment outcomes[58]. Furthermore, the antioxidant properties of *P. oleracea* can protect the gastrointestinal mucosa from the toxic effects of chemotherapy, reducing side effects, such as mucositis and improving the quality of life for patients undergoing treatment[59]. The ability of ZnO-NPs to enhance drug delivery and reduce toxicity makes them a promising adjunct to standard colorectal cancer therapies[60].

5.4. Prostate Cancer

Prostate cancer is one of the most common cancers among men, particularly in older adults[61]. Advanced prostate cancer, characterized by metastasis and resistance to hormone therapy, is associated with high mortality rates and limited treatment options[62]. ZnO-NPs synthesized with *P. oleracea* have shown potential in targeting prostate cancer cells through mechanisms, such as ROS-mediated apoptosis and inhibition of androgen receptor signaling[63]. The selective cytotoxicity of these nanoparticles allows for the targeted killing of cancer cells while sparing normal prostate cells, reducing the risk of side effects and improving treatment outcomes[64]. In addition to their direct anti-cancer effects, the anti-inflammatory properties of *P. oleracea* compounds may help reduce the chronic inflammation that contributes to prostate cancer progression[65]. By modulating the tumor microenvironment and reducing inflammation, ZnO-NPs synthesized with *P. oleracea* could offer a novel therapeutic approach for advanced prostate cancer, particularly when used in combination with hormone therapy or other targeted treatments[66].

5.5. Ovarian Cancer

Ovarian cancer is often diagnosed at an advanced stage, and the aggressive nature of the disease, combined with the development of resistance to chemotherapy, contributes to its high mortality rate[67]. The standard treatment for ovarian cancer involves platinum-based chemotherapy, but resistance to these drugs is a major obstacle to successful treatment[68]. ZnO-NPs synthesized using *P. oleracea* represent a promising strategy for overcoming chemotherapy resistance in ovarian cancer[69]. The nanoparticles can enhance the effects of platinum-based drugs by increasing drug uptake and sensitizing cancer cells to apoptosis[70]. The ROS-mediated mechanism of action, combined with the bioactive compounds in *P. oleracea*, helps to overcome drug resistance and improve patient outcomes[71]. Additionally, the antioxidant and anti-inflammatory properties of *P. oleracea* can reduce chemotherapy-induced toxicity, allowing for higher doses or prolonged treatment without increasing the risk of side effects[72]. This dual functionality makes ZnO-NPs a valuable addition to the therapeutic arsenal for ovarian cancer, potentially improving survival rates and quality of life for patients[73].

6. Challenges and Future Perspectives

6.1. Biocompatibility and Safety Concerns

Despite the promising therapeutic potential of ZnO-NPs, there are still challenges related to their biocompatibility and safety. While *P. oleracea* enhances the biocompatibility of ZnO-NPs, further research is needed to assess their long-

term safety and potential toxicity *in vivo*[74]. Studies should focus on the pharmacokinetics, biodistribution, and clearance of these nanoparticles to ensure they do not accumulate in healthy tissues or organs[75]. Understanding the interaction of ZnO-NPs with the immune system is crucial for their safe application in cancer therapy[76]. Potential immunogenicity and the risk of inducing an inflammatory response need to be carefully evaluated[77]. Future studies should aim to optimize the size, surface charge, and coating of ZnO-NPs to improve their biocompatibility and minimize potential side effects[78].

6.2. Scaling Up and Clinical Translation

Another significant challenge is the scalability of the green synthesis method using *P. oleracea*[79]. While laboratory-scale synthesis is feasible, producing large quantities of ZnO-NPs with consistent quality and characteristics is more challenging[80]. The scalability of the process must be addressed to facilitate the transition from bench to bedside[81]. Moreover, translating these findings into clinical applications requires extensive preclinical studies and clinical trials to establish efficacy and safety in humans[82]. Regulatory approval processes for nanomedicines can be lengthy and complex, requiring robust evidence of their therapeutic benefits and safety[83]. Collaboration between researchers, clinicians, and regulatory bodies will be essential to overcome these challenges and bring ZnO-NPs synthesized with *P. oleracea* into clinical use[84].

7. Key Findings

Several in vitro studies have demonstrated the cytotoxic effects of ZnO-NPs on different cancer cell lines. These studies showed that ZnO-NPs reduced cell viability in a dose-dependent manner. The IC50 values (the concentration required to inhibit 50% of cell growth) for ZnO-NPs were reported to range from 10 to 50 µg/mL, depending on the type of cancer cell. In animal models, ZnO-NPs synthesized from *P. oleracea* have shown promising anticancer activity. In a mouse model of breast cancer, ZnO-NPs inhibited tumor growth and induced significant apoptosis within the tumor tissue.

Synergistic Effects with Chemotherapeutic Agents: ZnO-NPs have been investigated for their potential to enhance the efficacy of conventional chemotherapeutic drugs. Studies suggest that ZnO-NPs, when used in combination with drugs, such as cisplatin or doxorubicin, can potentiate their anticancer effects, leading to reduced drug resistance and enhanced tumor cell death. ZnO-NPs are also being explored as carriers for targeted drug delivery. Due to their biocompatibility and ability to penetrate the cell membrane, ZnO-NPs can be functionalized with targeting ligands (e.g., antibodies and peptides) to direct them specifically to cancer cells, thereby reducing the side effects associated with traditional chemotherapy.

ZnO-NPs show significant promise in in vitro and *in vivo* cancer treatment, with cytotoxic effects observed across multiple cancer types. Their use in combination with other therapies (e.g., chemotherapy) can enhance therapeutic outcomes. As drug delivery vehicles, ZnO-NPs offer a potential strategy for targeted cancer therapy, improving drug localization and reducing off-target effects.

8. Future Research Directions

Future research should focus on several key areas to optimize the therapeutic potential of ZnO-NPs synthesized using *P. oleracea*:

- Optimization of Synthesis Conditions: Research should explore different extraction methods, plant parts, and synthesis conditions to enhance the yield and therapeutic properties of ZnO-NPs. Understanding the role of various bioactive compounds in *P. oleracea* during the synthesis process will allow for the fine-tuning of nanoparticle characteristics.
- Functionalization and Targeted Delivery: The functionalization of ZnO-NPs with targeting ligands, such as antibodies or peptides, could improve their selectivity and efficacy in targeting specific cancer cells. This approach could minimize off-target effects and enhance the therapeutic index of ZnO-NPs.
- Combination Therapies: Combining ZnO-NPs with other therapeutic modalities, such as immunotherapy, radiation therapy, or gene therapy, could offer synergistic effects and overcome the limitations of single-agent therapies. Exploring the potential of ZnO-NPs in combination with emerging cancer treatments could open new avenues for research and clinical application.
- *In Vivo* Studies and Clinical Trials: While in vitro studies provide valuable insights, *in vivo* studies are essential to understanding the behavior of ZnO-NPs in complex biological environments. Preclinical studies in animal models should be conducted to evaluate the pharmacokinetics, biodistribution, and therapeutic efficacy of ZnO-NPs. Successful preclinical outcomes will pave the way for clinical trials to assess their safety and effectiveness in cancer patients.

9. Conclusions

ZnO-NPs synthesized using *P. oleracea* represent a promising and innovative approach in cancer treatment. Their ability to selectively target cancer cells, enhance chemotherapy efficacy, and provide antioxidant protection to normal cells makes them a versatile therapeutic agent. While challenges related to biocompatibility, scalability, and clinical translation remain, continued research in this area holds great promise. The future of cancer therapy could see ZnO-NPs as a standard component of treatment regimens, offering patients a more effective and safer alternative to conventional therapies. With further optimization and rigorous clinical testing, ZnO-NPs synthesized with *P. oleracea* could revolutionize the way we approach cancer treatment, providing new hope for patients and healthcare providers alike.

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

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