“Betanin–Chitosan Coated ZnO Nanoparticles for Oral Cancer Therapy: A Comprehensive Review”

[1]Vinoth. A*, [1]Kalpana devi. M, [2]Parthiban K.G, [3]Sangameshwaran.B

[1]*Department of Pharmaceutics, SSM College of Pharmacy, Tamil Nadu, India*

[2]*Department of Pharmaceutics SSM College of Pharmacy, Tamil Nadu, India*

[3]*Principal, SSM College of Pharmacy College of Pharmacy, Tamil Nadu, India*

***Corresponding Author**

Vinoth.A

Department of Pharmaceutics,
SSM College of Pharmacy, Tamil
Nadu, India Phone: + 91
9360273883 Email:
vinothpharma883@gmail.com

Abstract

Oral cancer, primarily oral squamous cell carcinoma, remains a significant global health challenge due to its high incidence, aggressive progression, and limited success of conventional treatment strategies. Existing therapies such as chemotherapy and radiotherapy often suffer from poor specificity, systemic toxicity, and the emergence of drug resistance, highlighting the need for more effective and targeted approaches. In this context, nanotechnology has gained considerable attention for its potential to improve drug delivery and therapeutic outcomes.

Zinc oxide (ZnO) nanoparticles have been widely investigated for their inherent anticancer properties, particularly their ability to generate reactive oxygen species (ROS), leading to oxidative stress and apoptosis in cancer cells. To enhance their stability and biocompatibility, ZnO nanoparticles can be functionalized with chitosan, a natural polymer known for its biodegradability, mucoadhesive properties, and ability to improve cellular uptake. Furthermore, the incorporation of betanin, a natural pigment with antioxidant and anticancer activity, offers additional therapeutic benefits.

This review highlights the design, characterization, and anticancer potential of betanin–chitosan coated ZnO nanoparticles, with a focus on their application in oral cancer therapy. The synergistic effects of ROS generation, mitochondrial dysfunction, and DNA damage are discussed as key mechanisms underlying their anticancer activity. Additionally, the advantages of targeted delivery, controlled release, and reduced systemic toxicity are emphasized. Current challenges and future perspectives, including clinical translation and the development of advanced nanocarrier systems, are also addressed.

Overall, this nanocomposite system represents a promising strategy for improving oral cancer treatment outcomes.

Keywords: Oral Squamous Cell Carcinoma, Zinc Oxide Nanoparticles,Chitosan Functionalization, Betanin Nanocomposite.

1. Introduction

Oral cancer, predominantly oral squamous cell carcinoma (OSCC), represents a significant global health burden with high morbidity and mortality rates. It is particularly prevalent in developing countries due to risk factors such as tobacco use, alcohol consumption, and human papillomavirus (HPV) infection. (1)(2) Despite advances in diagnostic techniques and therapeutic strategies, the overall survival rate of oral cancer patients has not improved substantially over the past decades. Late-stage diagnosis, tumor recurrence, and metastasis remain major challenges, emphasizing the urgent need for more effective and targeted treatment approaches.

Conventional treatment modalities, including surgery, chemotherapy, and radiotherapy, are often associated with severe side effects, lack of selectivity, and damage to healthy tissues. Moreover, the development of drug resistance further limits the efficacy of chemotherapeutic agents. These limitations highlight the necessity for innovative therapeutic systems that can enhance drug delivery, improve targeting efficiency, and minimize systemic toxicity. (3)

In recent years, nanotechnology has emerged as a promising platform in cancer therapy due to its ability to engineer materials at the nanoscale with unique physicochemical properties. Nanoparticles offer several advantages, including enhanced permeability and retention (EPR) effect, improved drug solubility, controlled release, and targeted delivery to tumor tissues. (4) Among various nanomaterials, zinc oxide (ZnO) nanoparticles have gained considerable attention due to their intrinsic anticancer properties, primarily mediated through the generation of reactive oxygen species (ROS), leading to selective cancer cell death. (5)

To further enhance the biocompatibility and targeting efficiency of ZnO nanoparticles, surface modification with natural polymers such as chitosan has been widely explored. Chitosan is a biodegradable, biocompatible, and mucoadhesive polymer that facilitates improved cellular uptake and stability of nanoparticles, particularly in oral drug delivery systems. Additionally, the incorporation of natural bioactive compounds has gained increasing interest in nanomedicine. (6) Betanin, a betalain pigment derived from beetroot, exhibits potent antioxidant, anti-inflammatory, and anticancer properties, making it a suitable candidate for combination therapy. (7)

The integration of ZnO nanoparticles with chitosan coating and betanin functionalization represents a novel and synergistic nanotherapeutic approach for oral cancer treatment. This multifunctional system combines the cytotoxic effects of ZnO nanoparticles, the delivery efficiency of chitosan, and the therapeutic potential of betanin, offering a promising strategy to overcome the limitations of conventional therapies.

2. ORAL CANCER: Current Scenario

Oral cancer is a major malignancy within the head and neck region, with oral squamous cell carcinoma (OSCC) representing the predominant form. It remains a significant clinical concern due to its aggressive progression, high likelihood of recurrence, and potential for metastasis. The incidence is notably higher in developing countries, where lifestyle habits and limited access to early diagnostic services often result in late-stage detection and poor clinical outcomes**.**

2.1.Causes and Risk Factors

The occurrence of oral cancer is influenced by multiple environmental and biological factors. Tobacco use is considered the most critical risk factor, whether in smoked or smokeless forms, as it exposes oral tissues to carcinogenic substances that can induce genetic alterations over time. (8) Alcohol consumption further increases this risk by enhancing mucosal permeability, allowing harmful compounds to penetrate more easily.

In addition, infection with high-risk strains of human papillomavirus (HPV), particularly HPV-16, has been identified as a significant contributing factor. HPV-related carcinogenesis is associated with disruptions in normal cell cycle control. Other factors such as poor oral hygiene, chronic mechanical irritation, nutritional deficiencies, and genetic susceptibility also play supportive roles in disease development. (9)

2.2.Limitations of Chemotherapy

Chemotherapy is commonly used in the management of oral cancer, either alone or alongside surgery and radiotherapy. However, its effectiveness is often limited by several drawbacks. A major concern is its lack of selectivity, as anticancer drugs can affect both malignant and healthy cells, leading to adverse effects such as mucositis, immune suppression, and gastrointestinal complications. (10)

Another important issue is the development of multidrug resistance, where cancer cells gradually become less responsive to treatment. This can result in reduced therapeutic efficacy and increased chances of recurrence. (11) Additionally, challenges such as poor drug solubility, rapid elimination from the body, and insufficient accumulation at the tumor site further limit treatment success. (12)

These challenges emphasize the need for improved therapeutic approaches that can provide targeted delivery and minimize systemic toxicity. (13) In this regard, nanotechnology-based systems are gaining attention as potential alternatives to overcome the limitations associated with conventional chemotherapy. (14)

3. ZnO Nanoparticles in Cancer Therapy

Zinc oxide (ZnO) nanoparticles have emerged as promising agents in cancer treatment due to their distinctive physicochemical and biological properties. (15) Their nanoscale size enables efficient interaction with cellular systems and promotes accumulation in tumor tissues. (16) In addition, ZnO nanoparticles are relatively easy to synthesize, cost-effective, and can be modified with various coatings to improve stability and targeting, making them suitable for biomedical applications. (17)

3.1.Properties of ZnO Nanoparticles

ZnO nanoparticles exhibit several characteristics that support their use in cancer therapy. Their small size and large surface area enhance cellular uptake and allow effective interaction with biomolecules. (18) They also possess semiconducting properties, which contribute to their ability to generate reactive oxygen species (ROS). (19) Furthermore, ZnO nanoparticles can be functionalized with polymers or bioactive compounds to improve biocompatibility and therapeutic efficiency. (20) These features make them versatile platforms for drug delivery and anticancer activity.

3.2.Mechanism of Anticancer Activity

The anticancer activity of ZnO nanoparticles is mainly associated with the induction of oxidative stress. They generate reactive oxygen species such as superoxide and hydrogen peroxide, which disrupt the cellular redox balance and damage essential biomolecules, including DNA, proteins, and lipids. (21)

This oxidative stress leads to the activation of apoptosis, a programmed cell death process. ZnO nanoparticles can cause mitochondrial dysfunction, resulting in the release of apoptotic factors and activation of caspase enzymes. (22) In addition, they may interfere with the cell cycle, inhibiting cancer cell proliferation. The combined effects of ROS generation, apoptosis induction, and cell cycle arrest contribute to their effectiveness against cancer cells.

4. Chitosan-Based Nanocarriers

Chitosan-based nanocarriers have gained considerable attention in drug delivery due to their biocompatibility, biodegradability, and low toxicity. Chitosan, a natural polysaccharide derived from chitin, possesses unique physicochemical properties that make it highly suitable for biomedical applications. Its cationic nature allows strong interaction with negatively charged biological membranes, enhancing cellular uptake and improving the delivery of therapeutic agents. (23)

4.1.Drug Delivery Advantages

Chitosan offers several advantages as a drug delivery material. It can encapsulate a wide range of therapeutic agents, including small molecules, proteins, and natural compounds, thereby improving their stability and solubility. (24) Additionally, chitosan-based nanoparticles enable controlled and sustained drug release, which helps maintain therapeutic concentrations over an extended period. (25)

Another key benefit is its ability to enhance drug absorption by temporarily opening tight junctions between epithelial cells. (26) This property facilitates improved permeability and bioavailability of drugs. Furthermore, chitosan can be easily modified chemically, allowing the attachment of targeting ligands or functional molecules to enhance specificity and therapeutic performance. (27)

4.2.Oral Targeting Potential

Chitosan is particularly advantageous for oral cancer applications due to its strong mucoadhesive properties. It can adhere to the mucosal surfaces of the oral cavity, prolonging the residence time of the drug delivery system at the target site. (28) This localized retention increases drug concentration at the tumor region while reducing systemic exposure and associated side effects. (29)

In addition, the positive surface charge of chitosan nanoparticles promotes interaction with negatively charged cancer cell membranes, facilitating enhanced cellular uptake. This makes chitosan-based systems highly effective for targeted delivery in oral cancer therapy. (30) Overall, the combination of mucoadhesion, improved permeability, and controlled release makes chitosan an ideal carrier for developing advanced nanotherapeutic systems.

5. Betanin–Chitosan ZnO Nanoparticles

The integration of zinc oxide (ZnO) nanoparticles with chitosan coating and betanin incorporation represents a novel and multifunctional nanotherapeutic platform for oral cancer treatment. (31) This hybrid system combines the intrinsic anticancer properties of ZnO with the biocompatibility of chitosan and the bioactivity of betanin, resulting in enhanced therapeutic performance. Such a design aims to overcome the limitations of conventional therapies by improving targeting efficiency, stability, and overall anticancer efficacy.

5.1.Design Strategies

The development of betanin–chitosan ZnO nanoparticles typically involves a multi-step approach. Initially, ZnO nanoparticles are synthesized using chemical or green methods. (32) These nanoparticles are then coated with chitosan, which improves their stability, dispersibility, and compatibility with biological systems. The chitosan layer also provides functional groups that facilitate the loading of bioactive compounds. (33)

Betanin is subsequently incorporated into the chitosan-coated ZnO nanoparticles through electrostatic interactions or adsorption mechanisms. This design ensures effective encapsulation of betanin while protecting it from degradation (34). Additionally, the chitosan coating can enable controlled and pH-responsive release of betanin, particularly in the slightly acidic tumor microenvironment, thereby enhancing targeted delivery.

5.2.Synergistic Effects

The combined system exhibits a synergistic anticancer effect due to the complementary roles of its components. ZnO nanoparticles contribute to the generation of reactive oxygen species (ROS), which induce oxidative stress and damage cancer cells. At the same time, betanin provides antioxidant and anticancer properties, modulating cellular pathways and enhancing apoptosis. (35)

Chitosan plays a crucial role by improving cellular uptake and retention at the tumor site through its positive charge and mucoadhesive nature. This leads to increased accumulation of the nanocomposite in cancer cells, thereby amplifying therapeutic efficacy. (36) The overall synergy results in enhanced cytotoxicity against cancer cells while potentially reducing harmful effects on normal tissues.

Comparison with Other Nanocarrier Systems

Compared to conventional drug delivery systems, betanin–chitosan ZnO nanoparticles offer several advantages. Traditional chemotherapy lacks specificity and often causes systemic toxicity, whereas this nanocomposite enables more localized and controlled drug delivery. (37) In contrast to single-component nanoparticles, the combined system provides multiple mechanisms of action, including ROS generation, improved drug delivery, and bioactive compound activity.

Moreover, when compared to other polymer-coated nanoparticles, chitosan-based systems offer superior mucoadhesion and biocompatibility, making them particularly suitable for oral applications. (38) The inclusion of a natural compound like betanin further enhances safety and therapeutic potential, distinguishing this system from purely synthetic nanocarriers**.**

6. Mechanisms of Anticancer Action

The anticancer activity of betanin–chitosan coated ZnO nanoparticles is primarily driven by multiple interconnected cellular mechanisms. These nanocomposites exert their effects by inducing oxidative stress, disrupting mitochondrial function, and damaging genetic material, ultimately leading to cancer cell death. The combination of ZnO nanoparticles and betanin enhances these effects, while chitosan facilitates efficient delivery and cellular interaction.

6.1.Reactive Oxygen Species (ROS) Generation (39)

One of the key mechanisms involved is the production of reactive oxygen species (ROS). ZnO nanoparticles can generate ROS such as superoxide radicals and hydrogen peroxide within cancer cells. Elevated ROS levels disturb the cellular redox balance, causing oxidative stress. This leads to damage of essential biomolecules, including lipids, proteins, and nucleic acids, thereby impairing normal cellular functions. Cancer cells, which already exhibit higher basal oxidative stress, are particularly vulnerable to further ROS-induced damage.

6.2. Mitochondrial Dysfunction (40)

Excessive oxidative stress caused by ROS can directly affect mitochondrial integrity. The mitochondria play a central role in regulating cell survival and apoptosis. ZnO-based nanocomposites can disrupt the mitochondrial membrane potential, leading to the release of pro-apoptotic factors such as cytochrome c into the cytoplasm. This event triggers a cascade of intracellular signaling pathways that activate caspase enzymes, ultimately resulting in programmed cell death. The presence of betanin may further influence these pathways by modulating oxidative stress and enhancing apoptotic signaling.

6.3.DNA Damage and Fragmentation (41)

Another important mechanism is the induction of DNA damage. Increased ROS levels can cause breaks in DNA strands and interfere with replication and transcription processes. This damage activates cellular repair mechanisms; however, when the extent of damage exceeds repair capacity, it leads to DNA fragmentation and cell death. The accumulation of such genetic damage prevents cancer cells from proliferating and contributes to the overall anticancer effect of the nanocomposite system.

7. Future Perspectives

The development of betanin–chitosan coated ZnO nanoparticles represents a promising direction in oral cancer therapy; however, further advancements are required to translate these systems from laboratory research to clinical application. Future research should focus on improving targeting efficiency, validating therapeutic outcomes through clinical studies, and designing more advanced nanocarrier systems. (42)

7.1Targeted Delivery

Enhancing the specificity of drug delivery remains a key objective in nanomedicine. Future strategies may involve functionalizing the surface of nanoparticles with targeting ligands such as antibodies, peptides, or folic acid, which can selectively bind to receptors overexpressed on cancer cells. (43) This approach can improve the accumulation of nanoparticles at the tumor site while minimizing damage to healthy tissues. Additionally, stimuli-responsive systems that release drugs in response to changes in pH, temperature, or enzymatic activity within the tumor microenvironment offer significant potential for improving therapeutic precision. (44)

7.2Clinical Translation and Trials

Although numerous in vitro studies have demonstrated the anticancer potential of ZnO-based nanocomposites, there is a need for extensive in vivo investigations and well-designed clinical trials to establish their safety and efficacy in humans. Factors such as long-term toxicity, biodistribution, metabolism, and clearance must be thoroughly evaluated before clinical use. Bridging the gap between experimental research and clinical application remains a critical challenge in the development of nanoparticle-based therapies.

7.3Smart Nanocarrier Systems

The next generation of nanocarriers is expected to incorporate “smart” features that enable controlled and responsive drug delivery. (45) These systems may include multifunctional nanoparticles capable of simultaneous diagnosis and therapy (theranostics), real-time monitoring of drug release, and adaptive responses to the tumor environment. (46) Integration with advanced technologies such as biosensors and imaging agents could further enhance treatment outcomes. In this context, combining ZnO nanoparticles with biopolymers and natural compounds provides a strong foundation for developing efficient and intelligent nanotherapeutic platforms.

8. Conclusion

Oral cancer continues to pose a significant global health challenge due to its high incidence, aggressive progression, and limitations associated with conventional treatment strategies. The need for more effective, targeted, and safer therapeutic approaches has driven the exploration of nanotechnology-based systems in cancer management.

In this context, zinc oxide nanoparticles have demonstrated considerable potential owing to their intrinsic anticancer activity, particularly through the induction of oxidative stress and apoptosis. The incorporation of chitosan enhances the biocompatibility, stability, and targeting capability of these nanoparticles, especially for applications in the oral cavity due to its mucoadhesive properties. Furthermore, the inclusion of betanin, a naturally derived bioactive compound, adds an additional layer of therapeutic benefit through its antioxidant and anticancer effects.

The combined betanin–chitosan coated ZnO nanoparticle system offers a multifunctional platform that integrates efficient drug delivery with enhanced anticancer activity. Its ability to promote targeted delivery, induce multiple mechanisms of cancer cell death, and potentially reduce systemic toxicity makes it a promising candidate for future oral cancer therapy. Although further in vivo studies and clinical validation are necessary, this approach represents a significant step toward the development of advanced and effective nanotherapeutic strategies.

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