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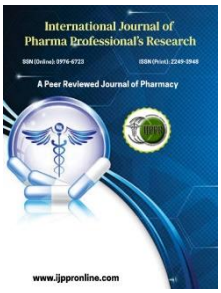

Bioactive-Based Nanocarriers for Targeting and Treating Cancer

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Bioactive-based nanocarriers, Cancer targeting, Precision medicine, Drug delivery, Tumor microenvironment, Therapeutic efficacy, Clinical translation

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ABSTRACT: Cancer therapy necessitates innovative approaches to target malignant cells while minimizing collateral damage to healthy tissues, and bioactive-based nanocarriers present a promising strategy by capitalizing on the distinct biological features of cancer cells for precise targeting and therapy delivery. This review highlights recent advancements in bioactive-based nanocarriers, exploring the unique characteristics of cancer cells, such as overexpressed receptors and altered metabolism, which serve as targets for selective drug delivery. Various nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles, are discussed in terms of their advantages and challenges. Strategies for functionalizing nanocarriers with bioactive ligands like antibodies, peptides, aptamers, and small molecules are examined to enhance specificity toward cancer cells. Preclinical and clinical studies demonstrate the efficacy and safety of these nanocarriers in overcoming biological barriers and reducing systemic toxicity. Challenges such as clinical translation and scalable manufacturing are outlined, along with future perspectives on integrating multifunctional platforms for combinatorial therapy. Bioactive-based nanocarriers hold immense potential for precision cancer therapy by enhancing drug delivery and therapeutic outcomes. Continued interdisciplinary research and collaboration are essential to optimize formulations, improve targeting efficiency, and translate these innovations into clinical practice, ultimately revolutionizing cancer treatment and improving patient outcomes.

1. Introduction

Cancer is a significant global health challenge, characterized by the uncontrolled growth of abnormal cells that can invade surrounding tissues and spread to other parts of the body. It is the second leading cause of death worldwide, responsible for an estimated 9.6 million deaths in 2018. The burden of cancer exerts immense physical, emotional, and financial strain on individuals, families, communities, and

healthcare systems globally. The disease can originate in almost any organ or tissue of the body, with common types including lung, prostate, colorectal, breast, and stomach cancer. The prevalence of cancer continues to rise, necessitating effective prevention, early detection, and treatment strategies to mitigate its impact.[1,2]

Innovative therapeutic strategies are crucial in addressing the challenges posed by cancer. These strategies aim to improve treatment outcomes, reduce side effects, and enhance patient care. Nanocarriers-mediated therapeutics have emerged as a promising approach for cancer therapy, offering improved drug delivery and therapeutic outcomes. Nanocarriers, such as bioactive-based nanoparticles, can enhance the bioavailability and efficacy of drugs by improving their solubility, stability, and targeted delivery to cancer cells. These innovative approaches hold the potential to revolutionize cancer treatment by increasing treatment efficacy, reducing toxicity, and improving patient outcomes.[3–6]

Bioactive-based nanocarriers are a cutting-edge approach in cancer therapy, leveraging nanoparticles to deliver bioactive compounds effectively to cancer cells. These nanocarriers can enhance the therapeutic effects of compounds like flavonoids and epigallocatechin gallate (EGCG) by improving their delivery and targeting. For instance, silibinin-loaded nanoparticles have shown enhanced cytotoxicity in oral carcinoma cells, while EGCG-loaded nanoparticles have demonstrated the ability to suppress tumor growth in breast cancer cells. Smart nanoparticles and bio-inspired nanoparticles are innovative strategies within this realm, offering controlled drug release and improved targeting of cancer cells. These advancements in nanotechnology hold great promise for the future of cancer treatment, offering more effective and targeted therapies for patients.[7,8]

1.1 Characteristics of Cancer Cells

Cancer cells exhibit distinct characteristics that differentiate them from normal cells. These characteristics include:

- **Uncontrolled Growth:** Cancer cells grow and divide at an abnormally rapid rate, are poorly differentiated, and have abnormal membranes, cytoskeletal proteins, and morphology. They exhibit self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death, limitless replication potential, sustained angiogenesis, and the ability for tissue invasion and metastasis.[9]
- **Genetic Mutations:** Cancer cells accumulate genetic mutations that drive their abnormal behavior, leading to uncontrolled growth and resistance to normal regulatory mechanisms.[10]
- **Immortality:** Cancer cells can evade apoptosis, allowing them to live longer compared to normal cells.[11]
- **Abnormal Appearance:** Cancer cells appear different under a microscope, showing variations in size, shape, and nucleus structure compared to normal cells.[12]

1.1.2 Overexpressed Receptors

- **Self-Sufficiency in Growth Signals:** Cancer cells acquire an autonomous drive to proliferate by activating oncogenes like ras or myc, leading to uncontrolled growth.[13,14]
- **Insensitivity to Growth-Inhibitory Signals:** Cancer cells inactivate tumor suppressor genes that normally inhibit growth, contributing to their uncontrolled proliferation.[15]

1.1.3 Altered Metabolism

- **Limitless Replication Potential:** Cancer cells activate specific gene pathways that

render them immortal, allowing them to continue dividing indefinitely.[16]

- **Sustained Angiogenesis:** Cancer cells acquire the ability to stimulate the growth of blood vessels to supply themselves with nutrients and oxygen, supporting their rapid growth[17]

1.1.4 Tumor Microenvironment

- **Tissue Invasion and Metastasis:** Cancer cells acquire the capacity to migrate to other organs, invade other tissues, and colonize these organs, leading to their spread throughout the body.[18]

- **Angiogenesis:** Tumors can secrete chemical signals that stimulate angiogenesis, the process of forming new blood vessels to support tumor growth.[19]

- **Immune Evasion:** Cancer cells can hide from the immune system and even manipulate immune cells to support their survival and growth.[20]

These characteristics collectively contribute to the aggressive and uncontrolled nature of cancer cells, highlighting the fundamental differences between cancerous and normal cells in Figure 1.

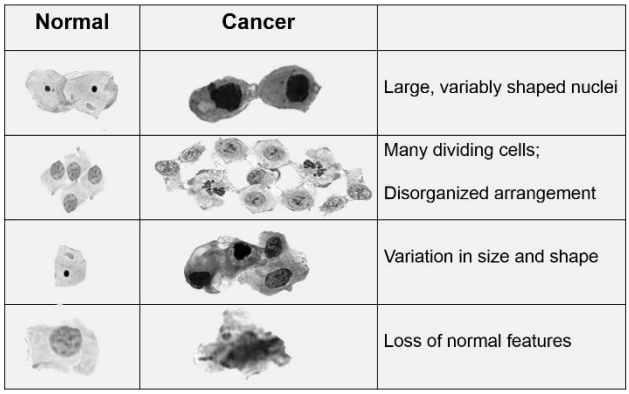

Figure 1: Differences Between Cancerous and Normal Cells

2. Types of Bioactive-Based Nanocarriers

- **Lipid-Based Nanocarriers:** Lipid-based nanocarriers, such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), are widely used in drug and food-based delivery systems.[21,22] They have the advantages of well-controlled release, enhanced distribution, and increased permeability. Lipid-based nanocarriers are more and more widely used in the area of novel nano-pharmaceutical or food-based design.[23]

- **Polymer-Based Nanocarriers:** Polymer-based nanocarriers, such as polymeric nanoparticles, are also used in drug delivery and diagnostics. They have high surface-to-volume ratio, enhanced electrical conductivity, superparamagnetic behavior, spectral shift of optical absorption, and unique fluorescence properties.[24]

- **Micelles:** Micelles are used in drug delivery systems to increase the solubility of hydrophobic drugs. They are formed by self-assembly of amphiphilic molecules in aqueous solutions. Micelles can be used to improve the bioavailability of poorly soluble drugs and to target drugs to specific sites in the body.[25]

- **Phytosomes:** Phytosomes are a type of nanocarrier that is used to enhance the bioavailability of plant-derived bioactive compounds. They are formed by complexing the bioactive compound with a phospholipid, which improves its absorption and bioavailability.[26,27]

- **Lipid-Polymer Hybrid Nanoparticles:** Lipid-polymer hybrid nanoparticles are a type of nanocarrier that combines the advantages of both lipid-based and polymer-based nanocarriers. They have high drug loading capacity, stability, and controlled release properties.[28]

- **Dendrimers:** Dendrimers are highly branched nanocarriers that can be used to deliver drugs, genes, and imaging agents. They have a well-defined structure, high drug loading capacity, and controlled release properties.[29]
- **Metallic Nanoparticles:** Metallic nanoparticles, such as gold and silver nanoparticles, are used in drug delivery, diagnostics, and imaging. They have unique optical and electrical properties that make them useful for various biomedical applications.[30,31]
- **Carbon-Based Nanoparticles:** Carbon-based nanoparticles, such as carbon nanotubes and graphene, are used in drug delivery, diagnostics, and imaging. They have high drug loading capacity, stability, and controlled release properties.[32]
- **Virus-Like Particles:** Virus-like particles are nanocarriers that mimic the structure of viruses but do not contain any genetic material. They can be used to deliver drugs, genes, and imaging agents. Virus-like particles have high immunogenicity and can be used as vaccines.[33]
- **Exosomes:** Exosomes are nanovesicles that are secreted by cells and can be used to deliver drugs, genes, and imaging agents. They have low immunogenicity and can be used to target drugs to specific sites in the body.[30]

These types of nanocarriers have been used to deliver various bioactive compounds, such as drugs, genes, and imaging agents, for various biomedical applications, including cancer therapy, infectious disease treatment, and vaccine development. However, the safety and efficacy of these nanocarriers should be thoroughly evaluated before their clinical application.[29]

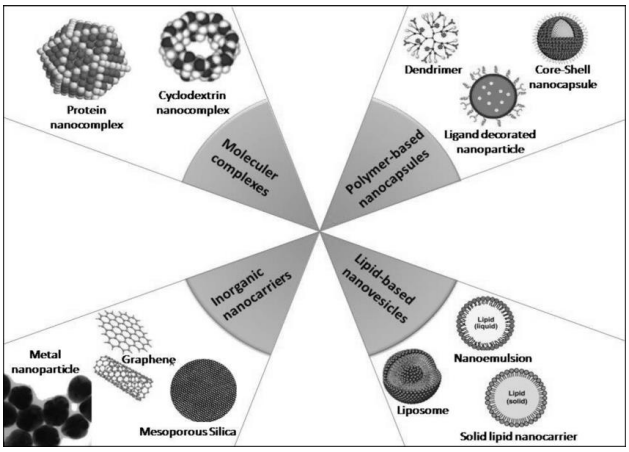

Figure 2: Types of Bioactive-Based Nanocarriers

3. Functionalization strategies

Functionalization strategies play a pivotal role in enhancing the specificity and efficacy of bioactive-based nanocarriers for cancer targeting and treatment.[34,35] These strategies encompass the utilization of various bioactive ligands, including antibodies, peptides, aptamers, and small molecules, to confer targeting capabilities to the nanocarriers. The rational design principles guiding ligand selection are paramount in ensuring optimal binding affinity and specificity towards cancer cells, taking into account factors such as receptor expression profiles and tumor microenvironment characteristics.[36,37] Additionally, conjugation strategies facilitate the precise coupling of bioactive ligands to the surface of nanocarriers, ensuring stable attachment while preserving ligand functionality. Techniques such as chemical conjugation, click chemistry, and biotin-streptavidin interactions are commonly employed to achieve efficient ligand conjugation. By employing these functionalization strategies, bioactive-based nanocarriers can be tailored to selectively target cancer cells, thereby enhancing drug delivery efficiency and therapeutic efficacy while minimizing off-target effects.[38,39]

4. Advantages of Bioactive-Based Nanocarriers for Cancer Therapy

- **Enhanced specificity towards cancer cells**: Bioactive-based nanocarriers can be functionalized with specific ligands that target receptors overexpressed in cancer cells, leading to increased drug accumulation in tumor tissue and reduced toxicity to normal cells.[40]

- **Targeted drug delivery**: Nanocarriers can protect the drug molecules against hydrolytic and enzymatic degradation, prolong circulation time, and ameliorate its therapeutic benefits.[41]

- **Overcoming biological barriers**: Nanocarriers can overcome biological barriers, such as the cell membrane and the extracellular matrix, allowing for efficient drug delivery to the tumor site.[42–44]

5. Challenges of Bioactive-Based Nanocarriers for Cancer Therapy

- **Challenges in scalability and manufacturing**: The production of nanocarriers at a large scale and their translation into clinical applications face several challenges, including the need for standardized manufacturing processes, quality control, and regulatory compliance.[45]

- **Complexity and heterogeneity**: The complexity and heterogeneity of cancer cells and their microenvironment can affect the efficacy of nanocarriers, requiring a better understanding of the mechanisms of drug delivery and resistance.[46]

- **Toxicity and immunogenicity**: The potential toxicity and immunogenicity of nanocarriers need to be carefully evaluated, as they can affect the safety and efficacy of the therapy.[47]

6. Preclinical and Clinical Studies

Preclinical and clinical studies play a crucial role in evaluating the efficacy, safety, and translational potential of bioactive-based nanocarriers for cancer targeting and treatment. These studies involve rigorous assessments aimed at elucidating the therapeutic benefits of nanocarrier-mediated drug delivery while mitigating potential adverse effects.[48]

Efficacy and safety assessments are conducted in preclinical models, including cell culture systems and animal models, to investigate the nanocarriers' ability to effectively target cancer cells and deliver therapeutic payloads. These assessments typically involve in vitro studies to evaluate cellular uptake, cytotoxicity, and pharmacokinetic properties, as well as in vivo studies to assess tumor accumulation, biodistribution, and antitumor efficacy. Additionally, preclinical studies also examine potential off-target effects and systemic toxicity to ensure the safety of nanocarrier formulations. 49,50Clinical studies further validate the efficacy and safety of bioactive-based nanocarriers in human subjects. Phase I trials focus on dose escalation and safety assessments, while phase II trials assess preliminary efficacy in specific cancer populations. Phase III trials involve large-scale, randomized controlled trials to evaluate the therapeutic benefits of nanocarrier-based therapies compared to standard-of-care treatments. These studies also investigate parameters such as overall survival, progression-free survival, and quality of life outcomes.[51,52]

The enhancement of therapeutic outcomes is a key objective of preclinical and clinical studies, aiming to demonstrate the superiority of nanocarrier-based approaches over conventional therapies. By optimizing drug delivery efficiency and enhancing tumor targeting, bioactive-based nanocarriers have the potential to improve

treatment efficacy, leading to better disease control and prolonged patient survival.[53]

Furthermore, bioactive-based nanocarriers offer the potential to reduce systemic toxicity associated with conventional chemotherapy by minimizing drug exposure to healthy tissues. Through targeted delivery to cancer cells and the tumor microenvironment, nanocarriers can enhance therapeutic efficacy while minimizing off-target effects, thereby improving the overall safety profile of cancer treatments.

Overall, preclinical and clinical studies provide critical evidence supporting the use of bioactive-based nanocarriers for cancer targeting and treatment, demonstrating their potential to enhance therapeutic outcomes while reducing systemic toxicity and improving patient outcomes.[48,51]

7. Future perspectives

Future perspectives in the field of bioactive-based nanocarriers for cancer targeting and treatment hold tremendous promise for advancing precision medicine and improving patient outcomes. Several key areas warrant attention to realize the full potential of these innovative therapeutic approaches.

Translation to clinical settings represents a critical step in bridging the gap between preclinical research and real-world applications. Efforts should focus on optimizing nanocarrier formulations for scalability, reproducibility, and regulatory compliance to facilitate clinical trials and eventual commercialization. Collaboration between researchers, clinicians, pharmaceutical companies, and regulatory agencies is essential to navigate the complex process of clinical translation and ensure the safe and effective deployment of nanocarrier-based therapies in clinical practice.54

Multifunctional platforms offer exciting opportunities for synergistic and personalized cancer therapy. By integrating multiple therapeutic modalities, such as chemotherapy, immunotherapy, and targeted therapy, into a single nanocarrier system, multifunctional platforms can enhance treatment efficacy while minimizing drug resistance and off-target effects. Additionally, the incorporation of diagnostic imaging agents enables real-time monitoring of treatment response and disease progression, facilitating personalized treatment adjustments for optimal outcomes.[55]

Integration with emerging technologies holds the potential to revolutionize cancer therapy by harnessing the power of artificial intelligence, nanotechnology, and precision medicine. Advanced drug delivery systems, enabled by nanotechnology, can precisely target cancer cells while sparing healthy tissues, minimizing side effects, and improving therapeutic outcomes. Machine learning algorithms can analyze vast datasets to identify patient-specific biomarkers and predict treatment responses, guiding personalized treatment decisions for improved efficacy and patient outcomes. The future of bioactive-based nanocarriers for cancer targeting and treatment is bright, with exciting opportunities for innovation and advancement. By translating research findings into clinical practice, developing multifunctional platforms for combinatorial therapy, and integrating with emerging technologies, we can accelerate progress towards precision cancer medicine and improve the lives of cancer patients worldwide. Continued collaboration and interdisciplinary research efforts are essential to realize the full potential of these promising therapeutic approaches.[54,56]

8. Conclusion

Bioactive-based nanocarriers hold immense potential for precision cancer therapy by targeting the unique properties of cancer cells for enhanced drug delivery, thus improving efficacy and minimizing off-target effects. This review highlights the strategies for functionalizing

nanocarriers with bioactive ligands, which enhance tumor specificity and therapeutic outcomes. Realizing their full clinical potential requires ongoing interdisciplinary research and collaboration to optimize formulations and improve targeting efficiency. The future of precision cancer therapy is promising with these advancements, potentially revolutionizing treatment through personalized, targeted approaches tailored to individual tumors, ultimately improving patient outcomes and quality of life.

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