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THE MODERN PERSPECTIVES OF NANOMATERIAL APPLICATIONS IN CANCER TREATMENT AND DRUG DELIVERY

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Abstract. Cancer, considered as one of the curses of the 21st century diseases, has been the subject of continuous exploration by scientists for many new treatment methods, utilizing different perspectives and approaches in treatment. However, due to the diversity in the causes of cancer, the organs affected by the disease and the types of cancer, the treatment process is quite challenging and cancer can reoccur after treatment. Unfortunately, a specific cure for this disease has not yet been found, making this topic still relevant and attracting the attention of scientists. Research is being conducted in the field of nanobiotechnology for cancer diagnosis, early detection and mitigation of side effects. Traditional cancer treatments include chemotherapy, radiotherapy, targeted therapy, hormone therapy, immunotherapy and gene therapy. However, limitations such as lack of specificity, cytotoxicity and resistance to multiple drugs create barriers for traditional cancer treatment methods. The emergence of nanotechnology has laid the foundation for a new era in cancer diagnosis and treatment. Nanoparticles (NPs) in the size range of 1-100 nm offer specific advantages in cancer treatment due to their biocompatibility, reduced toxicity, enhanced stability, improved permeability and retention effect and precise targeting.

Keywords: *Nanomaterial, nanoparticle, drug delivery, cancer treatment.*

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1. Introduction

Nanoparticles are now used during chemotherapy and radiotherapy (Yu *et al*., 2022; Nasibova *et al*., 2015). In chemotherapy, carrier systems like liposomes, polymers and nanogels are used to transport drug molecules efficiently. Metal oxide nanoparticles are used in radiotherapy (Haque *et al*., 2023). The key to achieving real success in cancer treatment lies in delivering drugs to cancer cells without affecting healthy cells as much as possible. When this is achieved, significant improvements in the patient's quality of life and lifespan can be achieved. NPs are loaded with toxic substances, various drugs, DNA/RNA and imaging agents. Depending on the specific properties of the loaded active substance, the loading capacity of nanoparticles and even the release of the loaded substance at the target site vary (Hasanzadeh *et al*., 2017). Depending on this capability, they can be multifunctional and innovations in treatment can be achieved by adding active substances for different stages of the disease process. Additionally, combination therapy with substances acting through different mechanisms is possible. The amount of drug

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accumulated at the target site can be monitored through added biomarkers, enabling diagnosis and treatment simultaneously. Indeed, the immune system's fight against cancer is accelerated after the application of drug-loaded NPs (Huang *et al*., 2023).

2. Liposomes

Liposomes are small-sized vesicles with a special structure that can carry substances dissolved in water or oil. Phospholipid-based liposomes are preferred in cancer-related research because they are non-toxic to the body and are easily identifiable in the body. Their lack of toxic properties is due to their resemblance to cell membranes in terms of structure and composition (Nsairat *et al*., 2022).

NP-based liposomes can be rapidly regulated in the bloodstream by the mononuclear phagocytic system. Liposomes are used in in vivo drug delivery and are highly efficient. The first officially approved nano drug, Doxil, is composed of doxorubicin encapsulated in liposomes coated with a hydrophilic polymer, polyethylene glycol. Doxorubicin is used in cancer treatment, where Doxil carries it to the tumor and releases the drug over an extended period, reaching the tumor quickly and prolonging the process (Waterhouse *et al*., 2001). Therefore, it is used in cancer treatment. There are various forms of liposomes:

Immunoliposomes: What are their characteristics? Liposomes functionalized with antibodies are called immunoliposomes. Immunoliposomes can carry a specific drug dose themselves and selectively engage with a chosen cancer cell to deliver the drug there. Antibody fragments, glycoproteins, peptides, vitamins, oligonucleotide aptamers and targeting ligands can be used as targeting ligands. Liposomes sensitive to various factors are called smart liposomes (Bozzuto *et al*., 2015). They can be sensitive to pH, high temperature, enzymatic activity, light, sound, magnetic fields and electromagnetic waves. In other words, liposomes are categorized into these groups.

PH-sensitive liposomes: Research has shown that the pH on the surface of cancer cells differs from that of normal cell surfaces. The pH on the surface of cancer cells is relatively lower than that outside the cells. The principle based on pH consists of what? These liposomes are highly sensitive to the environment's pH and exhibit different reactions when the pH varies. When it comes to cancer treatment, liposomes open up due to pH differences, releasing the drug substance inside and spreading it around. Liposomes that are sensitive to temperature and heat are called thermosensitive liposomes. They have a specific chemical group that is sensitive to temperature and the molecule melts at high temperatures. Therefore, the liposome opens up, releasing its drug contents into the surroundings and specifically targeting the cancer tumor. It is possible to construct liposomes that are sensitive to high-activity enzymes such as proteases and phospholipases associated with cancer cells' surface, so that these liposomes are sensitive to enzymes and react when they encounter these enzymes. The liposome opens and the drug substance inside spreads to the cancer tumor (Zylberberg *et al*., 2016).

3. Nanogels

Nanogels, also known as hydrogel nanoparticles, are nano-sized hydrophilic cross-linked polymer networks. In the past decade, interest in using nanogels as drug carriers and their imaging agents has increased. Nanogels are water-resistant, easy to inject and highly biocompatible based on their external structure. They are used in specific drug

delivery, meaning they are designed to carry selected specific drug substances (Dheer *et al*., 2019). They have the ability to respond to light, magnetic fields, PH, various specific biomolecules, high temperatures, meaning they are sensitive to them. Through muco-adhesive polymers, they can remain in the body for a long time and transport various types of drugs. This means that it is possible to load them with multiple types of drugs at the same time. Of course, this is one of their superior features. PH-sensitive nanogels protect from swelling with the EPR effect. PH-sensitive nanogels collect drug molecules in cancer tumors with the EPR effect. Then, outside the cells and inside cancer tumors, they start to break down due to different PH and release drug substances freely from cancer tumors. Temperature-sensitive nanogels are also used in cancer treatment. In this case, the drug substances are placed in nanogels, which are then introduced into the body. For example, if Organism X's body is at 37°C, they are irradiated with green laser, raising the temperature above 50°C. As it rises above 50°C, the drug substances are released and spread to the tumor, starting to show positive effects against cancer (Attama *et al*., 2022).

4. Polymer nanomaterials

Polymer nanomaterials are well defined as “colloidal macromolecules” with a special structure formed by various monomers. The drug is either compressed or attached to the outer surface of NPs to create a controlled-release nanosphere or nanocapsule for drug delivery. Initially, Polymer Nanoparticles (PNPs) consisted of non-biodegradable polymers such as polyacrylamide, polymethyl methacrylate and polystyrene. However, their accumulation in the system and difficulty in removal led to toxicity issues. Biodegradable polymers such as polylactic acid, poly(amino acids), chitosan, alginate and albumin are currently used, reducing toxicity and improving drug release and biocompatibility have been observed. Research has shown that coating PNPs with polysorbates and utilizing their surface-active effect has been effective (Patra *et al*., 2018). The external coating of NPs enhances their interaction with the blood-brain barrier endothelial cell membrane. Studies have shown that nanocapsules loaded with indomethacin significantly reduce swelling size and increase survival time in a xenograft glioma model. This represents a growing area in the clinical development of polymer NPs containing anti-cancer drugs (Kavetskyy *et al*., 2020; Montazersaheb *et al*., 2023).

Polymer nanomaterials have several superior properties: Stability, Biocompatibility, Biodegradability, Surface modification, Active and passive transport and Continuous drug release depending on the surrounding environment. Polyhydroxyalkanoates (PHA), cyclodextrins (CD) and poly(lactic-co-glycolic acid) (PLGA) are the most commonly used polymer materials for nanoparticle production. Polymer nanoparticles used in cancer treatment primarily carry anti-cancer, i.e., anti-tumor, specific substances or molecules inside. They have a hydrophobic core to remain in the blood for a long time and move within the body for an extended period, covered with a hydrophilic layer externally (Ahmadkhani *et al*., 2017).

The expression rate of cathepsin**s** has been shown to impact the invasiveness and metastasis of various cancers, such as colon cancer, ovarian cancer and pancreatic cancer. These copolymers inhibit lysosomal cathepsin enzymes, disintegrate under its influence and ensure the accumulation of high concentrations of imaging agents and drugs in cancer cells. Additionally, these copolymers can also carry anticancer drugs. Cathepsins can be conjugated with a fluorophore substance activated by infrared light, thus enabling their use in imaging tumor lesions (Dheer *et al*., 2019).

Matrix Metalloproteinases (MMPs) play a significant role in cancer development, including metastasis and progression. In humans, they are classified based on specific substrates and cell localization properties, with 23 numbered types of MMPs. Collagens, gelatins and extracellular matrix components are considered the main substrates of the MMP family (Hosainzadegan *et al*., 2020).

Tyrosine Kinases are enzymes similar to protein tyrosine kinases (PTK) that do not possess catalytic activity but play an important role in signal transduction. Higher levels of expression have been observed in certain specific cancer types in humans, such as acute lymphocytic leukemia (ALL) and esophageal squamous cell carcinoma (ESCC) (Russo *et al*., 2021).

Membrane Receptors It is known that epidermal growth factor receptor (EGFR) is overexpressed on cancer cell membranes. The increased expression of EGFR is associated with resistance to treatment, as acknowledged by researchers. Conjugated polymer nanoparticles with anti-EGFR antibodies have been reported to carry anticancer drugs to high levels of cancer cell accumulation. It has been speculated that targeting cancer cells with high expression of EGFR membrane receptors using antibodies on the polymer surface can enhance cancer-killing activity (Piletsky *et al*., 2023).

Nanoparticles are also used in radiotherapy for cancer treatment. During radiotherapy, high-energy radiation, typically X-rays, gamma rays or charged particles, is used to induce swelling and death in cancer cells (Haque *et al*., 2023). Additionally, during radiotherapy, the radiation can damage the genetic information of cancer cells, leading them to undergo apoptosis or cell death. It's important to note that while radiotherapy targets cancer cells, it can also affect healthy cells, so the dosage must be carefully administered.

Nanoparticles can affect radiotherapy in two ways: They can activate cancer cells using electromagnetic radiation, leading to their death. They can carry chemical substances that accumulate in cancer cells, enhancing the effect of radiotherapy and making the radiation more effective in killing cells (Maleki Dizaj *et al*., 2021). An ideal nano material for cancer treatment should have the following functions: detecting, diagnosing and targeting cancer cells effectively. It has been found that X-ray activated nanoparticles, by creating reactive oxygen species, destroy cancer cells and this process is called photodynamic therapy. It is an anticancer process. The ideal nanomaterial intended for cancer treatment should carry out these functions: detecting and diagnosing cancer, as well as attacking tumor cells (Haque *et al*., 2023).

Colorectal cancer incidence does not differ significantly between men and women and it ranks third in cancer diseases. An increase in the activation of Bcl2 gene notes has been observed in colon cancer compared to normal tissues. RNA interference (RNAi) is a mechanism that stimulates the degradation of mRNA through siRNAs. Recent research has shown promising developments in cancer treatment by applying siRNA-gold nanoparticle complexes in various doses to DLD colon cancers with the goal of suppressing the activation of the Bcl-2 gene (Chung *et al*., 2021).

5. Gold Nanoparticles in Biomedicine

Gold NPs possess unique optical properties related to their size and shape. For example, spherical Au0 NPs with diameters of 10-25 nm absorb light in the 520 nm region, while gold nanorods absorb in the near-IR range (He *et al*., 2005). These properties make them suitable for in vivo diagnostics and therapy. Modified gold NPs

exhibit low immunogenicity and high biocompatibility. Particles sized 10-22 nm can be used as carriers for drug delivery (Huang *et al*., 2023). Gold NPs have been shown to enhance the immune response to viruses in vivo, particularly through their optical and electronic properties.Gold NPs are actively used in designing biosensors due to their unique electrical and optical properties and their ability to form strong complexes with biomolecules. Modified gold NPs based on graphene oxide have been designed for detecting various biomarkers, including localized surface antigens of colon cancer cells, in biosensors (Nasibova *et al*., 2017).

In recent years, gold NPs have become increasingly utilized in oncology. Researchers' growing interest in these particles is due to their unique optical and electron properties, such as surface plasmon resonance. The integration of diagnostic and therapeutic functions into one system (theranostics) allows for managing therapeutic responses, making both diagnostics and therapy significantly easier. It has been noted in the International Journal of Nanomedicine that gold nanoparticles illuminate the future of cancer therapy (Jain *et al*., 2012).

One specific protein that can be used as a marker for cancer diagnosis and treatment on the surface of many cancer cells is the epidermal growth factor receptor (EGFR). The selective effect of NPs on cancerous swellings may be related to the structural properties and growth of the swelling cells (Nasibova *et al*., 2021). Cancer cells grow rapidly and have significant gaps between and within their membranes, making it easier for NPs to enter the cell directly. Increased acidity within the swelling cell also aids in the targeted and timely release of drugs inside the affected organ. After binding to swelling cells, NPs are irradiated by a powerful IR laser. In response to the IR radiation from the laser, gold NPs emit ultrasound and thermal waves. Ultrasound irradiation is used for diagnostics (photoacoustic monitoring), while heat waves are used for photothermal therapy. The local heating caused by the encapsulated gold capsule enables targeted and timed release of drugs (Russo *et al*., 2021).

6. Magnetic Nanoparticles in Biomedicine

Nanoparticles with magnetic properties hold significant importance in medicine, especially in the context of applying external magnetic fields to remotely control them and structures built upon them. To fulfill the requirements for their biomedical use, magnetic nanoparticles need to: 1) establish a stable colloidal system in aqueous solutions and other biological media, 2) be capable of adjusting various parameters such as salt concentration, pH, temperature, etc. within defined intervals (Stueber *et al*., 2021). Due to their high reactivity, there is virtually no inert environment for magnetic nanoparticles. One notable characteristic of their behavior in biological settings is their tendency to aggregate, hence practical utilization focuses on their stabilization. Immobilization of nanoparticles on surfaces facilitates the immobilization of biomolecules and protects against their degradation under various influences. Studies have shown that immobilized nanoparticles maintain their stereometry and remain resistant to the effects of nucleases. When enzymes and proteins are immobilized on magnetic particles, their stabilization primarily involves maintaining conformational structures and preventing enzymatic degradation. Moreover, due to their small size, nanoparticle interactions do not induce denaturation of protein molecules, which is crucial for preserving functional activity and proximity to targets, such as in antibody targeting (Binandeh, 2022). Thus, significant

progress has been made in the medical application of magnetic nanoparticles. The main areas of biomedical application include:

1. Diagnostics and Research Tools: Utilized in biosensors, Magnetic Resonance Imaging (MRI), biomolecule markers, bioseparation, sample preparation and the study of molecular interactions.

2. Targeted Therapeutic Effects: Enabling targeted delivery of therapeutic molecules and controlled local hyperthermia, among other therapeutic interventions.

3. Development of Biological Vaccines: Contribution to the development of biological vaccines.

The idea of using magnetic targeting for the purposeful delivery of therapeutic agents (e.g., oligonucleotides, proteins, drugs) was proposed by Widder in 1978. This approach in targeted chemotherapy can significantly reduce drug dosage and associated side effects, neutralizing nonspecific negative effects on the organism. When anticancer drugs are attached to magnetic nanoparticles, they can be directed using external magnetic field forces, offering a promising avenue in cancer treatment. Several studies have explored the feasibility of delivering doxorubicin attached to the surface of nano-sized particles to experimental animal tumors (Manescu *et al*., 2021).

The use of various methods with nanomaterials for cancer prevention is undoubtedly expected to be further improved in the coming years (Khalilov *et al*., 2022). Currently, nanoparticles are utilized in chemotherapy and radiotherapy for cancer treatment. During chemotherapy, nanomaterials carry drug substances to target cancer cells. Liposomes, nanogels and polymers are among the nanostructures used in this process (Ahmadkhani *et al*., 2015). During radiotherapy, nanomaterials can destroy cancer cells through two different methods. In the first method, they can activate cancer cells with electromagnetic radiation, leading to their death. In the second method, nanoparticles themselves can carry chemical substances that accumulate in cancer cells, enhancing the effect of radiotherapy and causing cell destruction. Gold nanoparticles (NPs) possess enhanced light absorption and scattering characteristics, with their absorption spectrum character depending on their size and shape. Modified gold NPs exhibit low immunogenicity and high biocompatibility. Particles in the size range of 10-22 nm can be used as carriers for drug delivery (Khalilov *et al*., 2018). Due to their unique electrical and optical properties and the ability to form strong complexes with biomolecules, gold NPs are actively used in the design of biosensors. In recent years, gold NPs have increasingly been utilized in oncology, mainly due to their unique optical and electron characteristics, such as surface plasmon resonance. Researchers' growing interest in these particles is believed to be capable of revolutionary breakthroughs in cancer diagnosis and treatment. Integrating diagnostic and therapeutic functions into a single system (theranostics) allows for the management of therapeutic responses, significantly facilitating both diagnosis and therapy. It has been noted in the International Journal of Nanomedicine that gold nanoparticles illuminate the future of cancer therapy. The main areas of biomedical application for magnetic nanoparticles include: 1. Diagnostic and research tools (biosensors, MRI, biomolecular markers, bioseparation and sample preparation, studying molecular interactions). 2. Targeted therapeutic effects (delivery of therapeutic molecules, controlled localized hyperthermia). 3. Development of biological assays.

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