Review Article

Investigating the Anticancer Effects of Nanoparticles in Cancer Treatment

Abstract

Cancer is the main cause of death worldwide. The existing methods have not been able to respond to the treatment requirements of all types of cancer. The emergence of nanotechnology has had a deep impact on many areas of health care and scientific research. The purpose of this study was to review the therapeutic and anticancer effects of nanoparticles. This study is a review, and the articles that were published between 1990 and 2023 were examined. Searching for articles in this study was done in Scopus, Google Scholar, Science Direct, and PubMed databases. Due to the nanoparticle's advantages, including the ability to convey drugs, control drug release, reduce toxicity, and specific delivery of drugs to the target organ, these structures have attracted many researchers' attention. Because of these structures, nanotechnology has created a great potential for the treatment of cancer that can change from the study laboratory to the bedside of the patient. One of the possible concerns that limit the use of some nanoparticles for cancer treatment is their toxicity, which requires further study. Nevertheless, cancer treatments based on nanotechnology will continue to develop and lead to improved treatment outcomes.

Keywords: *Nanoparticles, Anticancer effects, Cancer, Cancer treatment*

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Introduction

Based on the World Health Organization report in 2014, cancer caused the death of 8.2 million people worldwide in 2012, and this number can reach more than 22 million by 2035.[1, 2] Along with radiotherapy and surgery, chemotherapy is the mainstay of cancer treatment. Chemotherapy is the most common treatment method to suppress the proliferation of metastasis, disease progression, and cancer cells. However, chemotherapy drugs not only destroy cancer cells but also damage normal body tissues and cause side effects. Therefore, antitumor drug carriers that Maintain or improve chemotherapy effectiveness while decreasing the reaction severity and side impact are very much needed. Nanoparticles that can adapt to different biological properties and be utilized in a wide range of applications provide a safer and more effective means of delivering chemotherapy.[3-6]

The nanoparticle's emergence in cancer treatment systems (such as recombinant proteins with antitumor properties and drug delivery) in the last decade has brought many hopes. The accumulation of nanoscale systems at the tumor site becomes possible due to the specific characteristics of the microenvironment around the tumor. Therefore, some nanoparticles can enhance the activity of cells of the endoplasmic reticulum system when they carry peptides or proteins and activate dendritic cells and macrophages. Activated dendritic cells and macrophages ingest the complex and process it, triggering more effective immune responses. These nanoparticles increase the response of the immune system to the target antigen and are effective in guiding and directing this system to produce a specific type of response. The use of these nanoparticles as an antigen carrier reduces antigenic toxicity and the amount of recombinant protein used, and as a result, the destructive effects of proteases on protein antigens are reduced. This strategy improves the efficiency of the target protein in inducing immune responses against tumors and is effective in advancing functional goals such as drug and protein delivery.[7-10]

Materials and Methods

This study is a review, and the articles that were published between 1990 and 2023 were examined. Searching for articles in this study was done in Scopus, Google

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Scholar, Science Direct, and PubMed databases. The found articles were reviewed, and those that were outside the scope of this study were excluded from the study.

Results and Discussion

Nanotechnology's emergence and its convergence with other fields, such as medical sciences, has attracted the attention of medical studies because of its potential applications in the treatment and diagnosis of diseases.[11, 12] Because of nanoparticle size (1-100 nm), they have a large ratio of surface-to-volume, which empowers them to absorb large amounts of drugs [13] and easily diffuse them by the bloodstream.[14] Their larger surface area and properties give them uniqueness because they improve their catalytic, optical, magnetic, and mechanical properties, thereby increasing their potential medicinal use.[13, 15] Nanotechnology provides the manipulation and production of materials at the nanometer scale. Therefore, it enables the creation of new methods for the diagnosis, treatment, control, and monitoring of biological systems. This nanotechnology application in the medical field is known as Nano medicine. There are different types of nanoparticles according to different sizes, shapes, compositions, and properties. Recently, different nanoparticles have been specially designed and can deliver nucleic acids (such as DNA and RNA to cells) and anticancer drugs. These nanoparticles can be classified as organic or inorganic, which are briefly explained in the following sections.[16]

Organic nanoparticles

Liposome

Liposomes have spherical structures and consist of a hydrophobic shell and hydrophilic core, which makes them capable of carrying hydrophilic and lipophilic drugs.[17] The liposomes used as nanoparticles for chemotherapy have many benefits, including high drug loading capacity and drug encapsulation efficiency, fewer side effects, good biocompatibility, sustained release effects, low immunogenicity, specific targeting, and good stability. Because their composition is similar to cell membranes, liposomes are more biocompatible than other synthetic materials.[18] The PEG-modified liposomes (second generation of liposomes) can effectively evade phagocytosis by the mononuclear macrophage system in vivo. In addition, liposomes have been used as nanocarriers for chemotherapy drugs in sarcoma, ovarian cancer, and breast cancer, and good findings have been obtained.[19] Recently, liposomes have been utilized to target CD90 or CD45 T cells in vivo and in vitro to realize appropriate immunotherapy. The most common strategy for targeting the receptors on the cancer cells' surface is to use a ligand or antibody specific to the receptor. For this purpose, the use of targeted ligands on liposomes specific to receptors on the surface of cancer cells, due to their involvement in cell absorption mechanisms, may increase the therapeutic response.[20] Depending on the number and size of layers of liposomes, they can be divided into three categories: Small Unilamellar Vesicles (SUVs), Large Unilamellar Vesicles (LUV), and Multi Lamellar Vesicles (LV). In addition, liposomes can be classified into 5 types in composition terms and mechanism inside the cell: Long-circulating liposomes, Immunoliposomes, Cationic liposomes, PH-sensitive liposomes, and Conventional liposomes.[21]

Micelle

Micelles are another class of lipid-based nanoparticles that have a hydrophilic shell and hydrophobic core (filled with therapeutic agents). Their distinctive features include long-term circulation in the blood, reduced side effects, and strong binding to target cells. Micelle formulations, including paclitaxel, doxorubicin, and cisplatin, have undergone clinical trials with some progress in phase II research. They have proven their effectiveness against different tumors and reduced side effects, making them promising for clinical application.[22] Because chemotherapeutic agents are usually insoluble in water and their therapeutic results are compromised using systemic toxicity and short circulation time, significant studies have been done during the last century to improve the therapeutic benefits and reduce these limitations of anticancer drugs. In the past decades, Nanocarriers such as nanoparticles, micelles, and liposomes made of different materials have been introduced as an attractive study field in cancer treatment. Micelles are broad carriers for water-soluble drug delivery.[23] Micelles have advantages such as being very small (10-100 nm) compared to other drug carriers, which is very important for targeting solid tumors. Various methods are used to load drugs inside micelles: (1) oil-in-water emulsion methods (O/W); (2) water-in-oil-in-water emulsion techniques (W/O/W); (3) direct dialysis; (4) solvent evaporation and (5) dry freezing/lyophilization.[24] Among the aforementioned methods, oil in water, direct dialysis, and Solvent evaporation are suitable for encapsulating hydrophobic drugs, while the water-in-oil-in-water technique is usually preferred for encapsulating more hydrophilic compounds. Micelles can be modified by ligands for active drug delivery to increase selectivity for cells increase tumor and intracellular drug delivery. On the other hand, reduces systemic toxicity and harmful side effects compared to non-targeted micelles for drug delivery (inactive and systemic chemotherapy).[25] When ligands are attached to micelles, their receptor binds on the cell membrane, and micelles enter the cell by endocytosis. With this method, a higher intracellular drug concentration is obtained. Micelles as a drug delivery system, because of their simplicity, their loading capacity with a wide range of insoluble drugs, their small size, and the possibility of developing and improving their areas, have attracted much attention.[26]

Polymer

Polymer-based nanoparticles form a huge part of nanomedicines. The most common polymers used to produce polymeric nanoparticles are PLGA (Poly lactic-co-glycolic acid), PGA (Polyglycolic acid), PLA (Polylactic acid), and PCL (Polycaprolactone), all of which are used to improve the efficacy of cancer treatment methods. Polymeric nanoparticles are prepared by various methods based on the application type and the type of drug encapsulated in them. Among the advantages of these nanoparticles are the characteristics of controlled and sustained release, size in cellular dimensions,

and biocompatibility with tissue and cells. These particles are suitable for carrying all kinds of pharmaceutical, protein, peptide, or nucleic acid molecules. In addition, the use of polymers in the targeted treatment of tumors has increased as a drug carrier due to the increase in the drug half-life and the reduction of side effects to other cells.[27] Drug delivery through different routes by polymer nanoparticles causes cancer cells to be more sensitive to therapeutic agents that can be delivered. Most of the drugs are passivated in polymer nanoparticles due to their hydrophilic properties. Hydrophobic molecules can loaded into hydrophobic parts of polymers or micelles, and hydrophilic molecules are trapped in hydrophilic compartments. Several drugs (such as nucleic acids) are loaded on the polymer nanoparticles' surface using chemical compounds or electrostatic forces. Another method is to combine drugs directly with the polymer through disulfide, amide, or ester bonds.[28]

Dendrimer

Dendrimers are very branched polymer macromolecules with uniform and suitable sizes and shapes. Their main structure includes three major components: the terminal groups, repetitive branching units, and the central core. Increasing the number of repetitive branched units related to the formation of spherical structures.[29] First, in 1978, dendrimers were created by two major routes: The convergent method introduced by Hawker and Frechet and the divergent method developed by Tomalia. Despite showing high potential for biological uses, especially as gene and drug delivery, all dendrimer classes have hemolytic and cytotoxic properties that increase concerns about them. Toxicity is related to the dendrimer properties and can be related to its core part, but it mainly depends on terminal groups as well.[30] Also, in some cases, these problems are depended on the strong cationic attributes of these nanoparticles. Surface correction of dendrimers can be helpful to improve their structure. Polyethylene glycol is often utilized to increase tumor accumulation and plasma circulation time by increased EPR (permeability and retention). Linking PEG chains with dendrimers has been shown to be a significant step in decreasing the toxicity of dendrimers.[31] In addition, protection of cationic charges using hydroxylation and acetylation can also reduce toxicity. Other reforms can affect cancer-targeting attributes. For example, after combining with folic acid and tumor-specific antibodies.[32] Nucleic acid therapies are currently receiving much attention due to their specificity and biocompatibility compared to general chemotherapy. However, nucleic acids are large hydrophobic molecules that cannot transude cell membranes and are assailable to enzymatic degradation in the bloodstream. Therefore, delivery systems that support nucleic acid molecules and release them to the desired sites are essential for successful nucleic acid treatments.

Two types of vectors are commonly utilized for nucleic acid delivery: non-viral and viral vectors. However, viral vectors raise concerns of oncological and immunological side impacts that hinder clinical applications. Reciprocally, non-viral vectors consist of synthetic or natural molecules that elicit a low immunogenic response. Such benefits make non-viral vectors ideal operating systems for nucleic acid delivery. Among these non-viral vectors, dendrimer-based vectors have received much attention as nucleic acid delivery systems for more than two decades. Several distinct attributes of dendrimers cause them to be preferable over other cationic polymers. The high amount of cationic charge offers multiple binding sites for nucleic acid molecules. The high cationic charge density in dendrimers plays a vital role in helping the DNA molecule complex. Nucleic acid protection against nuclease is one of the most important concerns regarding nucleic acid. Different groups have proven that combining dendrimers with nucleic acid molecules protects nucleic acid molecules against enzymatic degradation.[33]

Mineral nanoparticles

Gold nanoparticles

Gold nanoparticles (GNPs) have attracted much attention as a new substrate in biomedicine and nanobiotechnology due to their suitable surface absorption with molecular probes and impressive immunological and optical properties. Recently reported examples include control and detection of microorganisms, clinical chemistry, immunoassays, biosensors, gold nanoparticle applications in genomics, optical imaging and monitoring of tissues and biological cells, targeted delivery of drugs or other substances, and cancer cell photothermolysis. Gold nanoparticles are increasingly utilized not only in cell photometric tests and diagnostic tests but also for treatment purposes. Maryland University researchers utilized a colloidal gold vector in mice to deliver TNF to solid tumors. After intravenous injection, gold nanoparticles together with TNF are quickly collected in tumor cells, and spleen, liver cells, and other healthy organs are detected. The gold-TNF vector has low toxicity and a higher impact in decreasing tumor size than TNF alone due to the maximum antitumor reaction obtained by lower drug doses. A gold nanoparticle is the most popular nanoparticle. One of the reasons for the great attention to these nanoparticles and their utilization for medical and biological purposes is their easy and quick synthesis method. There are different methods for preparing gold nanoparticles, and all of them are based on the reduction of Au(III) salts, the most significant of which is HAuCl4. To prepare gold nanoparticles, suspend gold in a solvent. Different industrial and laboratory methods for preparing gold nanoparticles include photo biochemical methods, chemical sound methods, electrochemical methods, and chemical reduction methods. All of these methods use surfactants, soluble polymers, and different ligands as stabilizing agents.[34-36]

Silver nanoparticles

The unique chemical and physical properties of ANP (silver nanoparticles) have attracted the scientific community's attention because of their high thermal conductivity, antibacterial ability, chemical stability, and plasmonic properties.[37] Today, silver nanoparticles are utilized in several commercial products, including bandages, countertops, textiles, food, plastics, and soap. However, their action mechanism is still unknown. Some factors (purity, density, charge, size, chemistry, surface, and morphology) affect the silver nanoparticles in the field of biological activity.[38, 39]

Another significant property of silver nanoparticles is their role in cancer treatment. Silver nanoparticles are a promising method as an anticancer agent in investigation and diagnosis; they have several advantages with high effects against various cancer cell lines. Their better penetration and the possibility of tracking silver nanoparticles in the body make them a more efficient cancer treatment method with low risk compared to standard treatment methods. The unique attributes of silver nanoparticles, such as their high surface-to-volume ratio, easy synthesis, and optical properties, make them appropriate for cancer treatment.[40, 41] Silver nanoparticles can also attach to various molecules, such as DNA/RNA, to target various cells, polymers, or antibodies. These significant factors are vital for increasing the half-life for circulation in the body, which is essential in gene and drug delivery applications.[42] Furthermore, silver nanoparticles are utilized as a tool to ablate cancer cells because of their ability to convert radio frequency into heat.[43, 44] By inducing a change in the cell morphology, reducing the cell's metabolic activity, increasing the oxidative stress that leads to damage to the mitochondria, and producing reactive oxygen species (ROS), it ultimately causes damage to DNA. Examining the morphology of cancer cells shows that silver nanoparticle synthesis can increase cell death. If silver nanoparticles are combined with chitosan, it will increase the cell death rate.

Iron oxide nanoparticles

In the past decades, nanotechnology power has been utilized in countless fields, such as biomedical fields. Nanoparticles are solid colloidal particles with sizes of 1 to 100 nm. Because of the dimensions comparable to the cells of genes, proteins, and viruses, they can interact with the main biological processes. Recently, in nanomedical materials, much attention has been paid to the synthesis of different types of nanoparticles. Among them, magnetic nanoparticles made of iron, nickel oxides, or cobalt have special features, such as a high magnetic property and high surface-to-volume ratio, and provide the possibility of potential manipulation using an external magnetic field. Especially magnetic nanoparticles produced with a ferromagnetic material, i.e., IONPs (iron oxide nanoparticles) made of Maghemite (γ-Fe2 O3) and magnetite (Fe_3O_4), which have wide uses in medicine, including hyperthermia, targeted drug delivery, imaging, and They have biosensors.[45] In recent decades, much study has been conducted on iron oxide nanoparticle synthesis, and many results have explained efficient synthesis methods to biocompatible, shape-stable, produce controlled, and integrated iron oxide nanoparticles. The most popular methods, including sonochemical synthesis, microemulsion, hydrothermal synthesis, and coprecipitation, can lead to the synthesis of high-quality iron oxide nanoparticles. Furthermore, these nanoparticles can be created by other approaches such as electrochemical synthesis,[46] laser pyrolysis technique, and synthesis with bacteria or microorganisms (especially iron-reducing bacteria and magnetotactic bacteria). The high biocompatibility and low toxicity of magnetite nanoparticles cause the expansion of the use of magnetite nanoparticles in the delivery of targeted drugs. Using a field of external magnetic, nanoparticles can be directed to the desired tissue at the target site and release the drug. The targeted transfer of the drug leads to the reduction of the side impacts of the drug to the circumambient healthy tissues and decreases the required dose of the drug. To increase the magnetite nanoparticle biocompatibility for utilization in the drug delivery field, inorganic or organic coatings modify magnetite nanoparticles. The coating of magnetite nanoparticles with the right composition can control the drug delivery loading and release. In addition, appropriate coatings can decrease the nanoparticle's toxicity and increase their biocompatibility.[47]

Quantum dots

Quantum dots are semiconductor nanocrystals whose diameter is 2-10 nm and include elements of groups III to V or II to VI. Due to their size and special effect, quantum dots are one of the most popular nanocrystals with unique chemical and optical properties. Quantum dots offer many benefits over conventional fluorescent organic dyes and possess several useful properties for spectroscopy, including high resistance, long lifetime, and high fluorescence intensity to illumination. The luminescence of quantum dot-based multifunctional probes provides high sensitivity for targeted therapy and simultaneous molecular cancer imaging.[48] Since biocompatible quantum dots for in vitro imaging of cancer cells were introduced in 1998, researchers have combined quantum dot-based probes with cancer-specific antibodies, peptides, or ligands for imaging. They have been synthesized from cancer and laboratory diagnosis. Compared to immunohistochemistry, quantum dot immunohistochemistry (QD-IHC) is more accurate and valuable at low protein expression levels, can get a quantitative diagnosis, and can prepare more information for personalized therapy. With excellent implementation in biomedical imaging, quantum dot-based imaging has been one of the most promising methods for early cancer detection.[49] However, since QDs are hydrophobic, it is essential to combine QDs with biomolecules before use for surface modification, as QDs have a large surface area for binding such molecules. When combined with diagnostic agents, quantum dots can be utilized to diagnose and treat cancer with high specificity. Concerns about the toxicity of quantum dots are mainly related to their chemical composition, especially in the case of quantum dots containing heavy metal ions such as cadmium and mercury. To use quantum dots in clinical applications, they must show minimal toxicity. Overall, quantum dots are technological marvels with properties that may revolutionize cancer treatment and diagnosis. Currently, quantum dots are widely used in laboratory conditions, such as revealing cancer invasion, detecting cancer biomarkers in molecular pathology, providing a new approach to improve tumor heterogeneity and stratification Classification, treatment of cancer, and focusing on the tumor environment. However, several issues must be considered, including overall toxicity, clearance from the body, scalability of the synthesis protocol, environmental impact, manufacturing cost, etc.[50]

Conclusion

Because of the nanoparticle's advantages, including the ability

to reduce toxicity, carry drugs, specific delivery of drugs to the target tissue, and control drug release, these structures have attracted many researchers' attention. Because of these attributes, nanotechnology has created a high potential for the treatment of cancer that can change from the study laboratory to the bedside of the patient. One of the possible concerns that limit the use of some nanoparticles for cancer treatment is their toxicity, which requires further study. Nevertheless, cancer treatments based on nanotechnology will continue to develop and lead to improved treatment outcomes.

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Conflict of interest
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