Review Article

A Review of the Effectiveness of Using Nanoparticles in the Treatment and Diagnosis of Breast Cancer

Abstract

Cancer has been one of the main concerns of the health sector in recent years. The utilization of nanoparticles in medical science has created new possibilities for diagnosing, imaging tumors, and treating cancer in humans. This article reviews the utilization of inorganic and organic nanoparticles in cancer treatment and diagnosis. The method of gathering and summarizing the information was through the research conducted in connection with the structure of various types of nanoparticles and their application in imaging, diagnosis, and drug delivery systems in cancer treatment. From inorganic nanoparticles including quantum particles, which have a central core with magnetic attributes, for cancer imaging and detection, as well as from organic nanoparticle systems including dendrimers, aptamers, solid lipid nanoparticles, liposomes, and nanoparticles in transportation. Various drugs and ligands can be used. Aptamers are oligonucleotide or peptide molecules that bind to protein or target cells and are used in diagnosis, treatment, drug delivery, and molecular imaging. Also, nanobodies are antibody molecules that are widely utilized in cancer treatment and diagnosis. According to the obtained results, there are still limitations and challenges to the utilization of nanoparticles in medicine, however, it is vision that shortly nanoparticles will create a great revolution not only in oncology but also in medicine.

Keywords: *Breast cancer, Diagnosis, Treatment, Nanoparticles*

Kanchan Kohli[1], Bharti Mangla[1]*, Anzarul Haque[2], Sarwar Beg[1], Kuldeep Singh Patel[3], Majed Alrobaian[4]

[1]*Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, India.*
[2]*Department of Pharmacognosy, College of Pharmacy, Prince Sattam bin Abdul Aziz University, Alkharj, Saudi Arabia.*
[3]*Department of Pharmaceutical Chemistry, Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh, India.*
[4]*Department of Pharmaceutics and Industrial Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia.*

Address for correspondence:
Bharti Mangla, Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, India.
E-mail: bhartimangla@dpsru.edu.in

Introduction

Despite rapid treatment and diagnosis of breast cancer in some countries, this disease is the second most common cancer among women, which has reached 3 to 4 times in developing countries during the recent decades.[1, 2] More than 1.1 million cases of breast cancer are reported annually and more than 410,000 die from breast cancer.[3] There are many ways to treat breast cancer, including surgery, hormone therapy, and radiation therapy, each of which has many side effects and disadvantages, for example, tamoxifen, which is utilized in chemotherapy to treat breast cancer, causes cancer in endometrial tissue. Therefore, the need to create a system to deliver drugs to tumor tissue without side effects is felt.[1, 4]

The utilization of nanoparticles in the electronic, medical industries, and food is expanding. Preparation and creation of nano-sized particles (less than 100 nm) increases their surface area and increases the possibility of their reactions or organic and inorganic molecules.[5] The application of nanotechnology in medical science is the use of very small particles in the treatment and diagnosis of human cancers, which has introduced a new science branch in oncology called nano-oncology.[6] Nanoparticles for tumor imaging, showing cancer biomarkers or biomolecules, and targeting drug delivery have been rapidly developed. Chemotherapy drug stabilization, particularly of enzyme type, in polymer nanoparticles leads to an enhancement in their stability against proteases, pH, heat, and other factors that destroy their structure.[7] Semi-Conductor Fluorescent Nanocrystals such as particles Quantum dots that are conjugated with antibodies. They cause determination and marking of their exact rate in a small piece of breast tumor.[8] Other nano-sized particles such as Nano Cantiler and Nano Probes and coiled nanoparticles with special ligands are also used in cancer tumor imaging and peripheral metastasis determination.[9] It has been stated that nanoparticles that are conjugated with high magnetic force (Super Magnetic) and metalcore or biological antibodies against the gene of ERBB2 can meanwhile be beneficial in breast cancer treatment and imaging.[10]

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In recent years, nanotechnology advancement has led to the nanoparticles used in various fields of lace devices, electronics, disease diagnosis, industry, biosensors, drug delivery, photography, and the production of consumer products such as sports equipment, cosmetics, and sunscreens. The current study aimed to investigate the research conducted in connection with the structure of various types of nanoparticles and their application in imaging, diagnosis, and drug delivery systems in cancer treatment.

Materials and Methods

Pubmed, Scopus, and Google Scholar databases were used to collect and summarize information. Research and review articles using the MeSH template included malignancy, neoplasm, nanoparticles, cancer, nanotechnology, tumor imaging, aptamers, magnetic nanoparticles, biomarkers, liposomes, small interfering RNAs, diagnostic and therapeutic methods of breast cancer by nanobodies and nanoparticles.

Results and Discussion

Nanoparticles types used in medicine

The nanoparticles utilized are classified into two basic groups. Particles contain organic molecules as the basic building material and the second group usually has mineral and metal elements as the central core. Dendrimers, liposomes, emulsions, aptamers, carbon nanotubes, nanoparticles, solid lipid nanoparticles, and other polymers are known as organic particles.[11, 12]

Dendrimers and liposomes

Liposomes are utilized as drug carriers in the chemotherapy of different human tumors, such as breast cancer.[13] Dendrimers are utilized as a contrast agent in MRI and are an auxiliary agent for the detection of various pathological processes.[14]

Aptamers

Aptamers are peptide molecules and oligonucleotides (SSDNA or RNA) that bind to their intended molecules (proteins, small biomolecules, and even cells) with high specificity and affinity and are tools for diagnosing and treating diseases, such as cancer.[12] DNA aptamers compared to RNA aptamers are more stable. However, RNA aptamers are more flexible than DNA aptamers. Peptide aptamers are from a variable peptide loop that is related to a protein chain at the end. The variable loop has 10 to 20 amino acids and the protein scaffold has any protein with suitable solubility. Aptamers can also be utilized in drug delivery systems. These aptamers are attached to receptors of the cell surface and are dragged into the cell. siRNAs are utilized today as a new method of treatment. Their function is to persuade iRNA, which regulates certain gene expression. specific, Safe, and efficient delivery of siRNAs into special cells is of high importance in the therapy field.[15]

Nanobodies

Camels and sharks have antibodies that do not have a light chain and only contain a heavy chain, and they are called HCAbs (Heavy Chain Antibodies). These antibodies do not have CH1 domains, but they have CH3 and CH2 domains, which are very similar to conventional antibodies. Thus, the Fb part that binds to the antigen in conventional antibodies is confined to a second variable in HCAD antibodies, and as mentioned, it only contains the heavy chain, which is called HHV, and because its size is about nanometers (4 nm in height and 2 to 5 nm in diameter) are known as nanobodies and have many uses in nanotechnology.

Today, monoclonal nanobodies can be made in bacteria, and due to their size (small), compared to conventional antibodies they are more stable. They have great solubility, have great affinity, and are exclusive to their antigens. Thus, they have a great potential for cancer diagnosis and treatment.[3]

In Van Impe *et al*. studies on mice,[16] the utilization of nanobodies has caused the amount of mammary gland cancer cell metastasis to decrease in these mice.[16] In some breast cancers (20-30 %), it has been seen that the level of activity and expression of 2 surface antigens HER2 and HER1 increases.[17] By making nanobodies special to these two types of surface receptors, it is possible to diagnose and treat cancer.

Mineral nanoparticles

The most inorganic nanoparticle structure has a central core with magnetic, fluorescence, and electrical attributes with an organic protective coating on the surface. This outer layer guards the central part from the environment's decomposing agents and can connect with positively charged molecules and biomolecules that include thiol or amine groups by covalent or electrostatic bonding.[18]

Quantum Dots are fluorescent nanoparticles (10-20 nm) that include a central nucleus of hundreds to thousands of group II and VI elements atoms (including cadmium, titanium, selenide, and zinc) or group III (such as tantalum) and group V (indium) are.[19] Quantum particles include a zinc sulfide coating and a cadmium selenide central core, which is restricted by a ligand coating and amphiphilic polymer. Of course, the application of quantum particles in therapeutic applications and imaging in invasive conditions is limited because of the toxic effects of heavy metal nuclei.[20]

In the Surface Enhanced Raman Scattering technique which is a sensitive technique to determine the multiple molecules spectroscopic spectrum,[21] silver or gold metal is utilized to enhance the reporter molecule light sensitivity to determine the spectroscopic spectrum, and a silica surface layer is utilized to conjugate the protein.[22] The application of these nanoparticles is to find very low and specific concentrations of materials such as amphetamine sulfate in clonidal suspension.[23]

Supermagnetic nanoparticles are suitable for enhancing contrast and are utilized in MRI. The nanoparticles of Magnetic with an external coating of an organic substance

connected with a biomolecule are utilized to carry drugs in cancer treatment.[24]

The achievement of many targeted therapies related to the expression of particular genes or proteins in cancer cells. For instance, in breast cancer, the hormone receptor expression level is directly related to the progress of endocrine therapy, and overexpression of gene amplification or HER2 protein or both is a prerequisite for the use of the monoclonal antibody Trastuzumab.[25]

Tissue immunochemistry is the main method for characterizing the expression of HER2 or hormone receptors. The benefit of using quantum particles is to overcome these limitations. Individual quantum particles can bind to various antibodies for particular proteins. The resulting spectrum of quantum particles conjugated with various proteins is simultaneously characterized by spectroscopy. The fluorescent emission amount from these conjugated nanoparticles is related to protein expression.[8]

In short, by using conjugates of quantum particles and probes, it is possible to determine the number of multiple proteins meanwhile on a piece of small cancer samples or tumor, and the final treatment method according to these results becomes easy.[6]

Tumor imaging

Today, magnetic nanoparticles are utilized for their ability to create contrast in MRI, which has less toxicity and biological compatibility.[26] Supermagnetic nanoparticles (3-10 nm) are utilized as a contrast agent in bismuth nanoparticles and MRI is utilized as a contrast agent for CT. If the surface of bismuth nanoparticles is covered with polymer, they will be preserved from parsing and the tissues will be preserved from their toxicity. These nanoparticles demonstrated good stability in high concentration, they absorb a lot of X-rays, and their retention time in the blood reaches more than 2 hours. Thus, the ratio of the efficiency of these particles to their safety is better than iodinated substances in imaging. The use of quantum particles with infrared wavelength for non-invasive tumor imaging in vivo has been reported.[26]

Gao *et al*.[9] coated the surface of quantum particles using a three-membered amphiphilic copolymer of hydrophilic polymethacrylate parts, two hydrophobic poly butyl acrylate parts, and one polyethyl (acrylate) part. These polymers protect nanoparticles from decomposition and because they have molecules of polyethylene glycol, they amend the biological ability of quantum particles and also their intravascular circulation. Conjugating quantum particles with targeted antibodies against particular prostate membrane antigens causes human prostate cancer to be specifically labeled and the amount of quantum particle accumulation in the bone and liver marrow decreases. In addition, 3 polymers of 0.5-micrometer quantum particles with red, yellow, and green colors can be seen meanwhile in three various parts. Today, quantum nanoparticles are suggested in determining the degree of cancer and its early detection. The limitation of utilizing quantum particles is due to their toxicity, currently, this strategy is being expanded by reducing the particle's toxic effects.[27]

Simultaneous treatment and imaging

Nanoparticles that are connected with intended antibodies can be utilized for cancer treatment and diagnosis at the same time. Conjugation of targeted ligands is done using biotin and streptoavidin. This method is utilized to conjugate an anti-ERBB2 to a modified metal nanoparticle to form a nanoshell.[28] This system structure consists of a spherical nanoparticle that is dielectric in the core is made of silica and is restricted by a thin layer of gold. This nanoshell, which has a near-infrared emission spectrum, converts light into heat energy and acts thermally for tumor surgery or tumor removal. These nanoparticles, which generate heat under the influence of near-IR radiation, are a million times more effective than colored molecules. The heat they generate is more than essential to cause irreclaimable tissue harm, resulting in cell death. Targeted nanoshells are utilized for irreclaimable breast tumor removal in vivo.

Breast cancer treatment

Extensive research has been done to utilize nanoparticles that can support healthy tissues and have a lethal impact on cancer cells. For instance, liposomal anthracycline is utilized in the treatment of all types of breast cancer,[29] but its utilization is limited because of its toxic effects on the heart. This combination together with Trastuzumab, which is a methocetal antibody against ERBB2, has a good effect.[30]

It has been stated that liposome and pglinide liposomes including Doxorubicin are utilized in the metastatic breast cancer treatment.[31] Also, nanoparticles that contain Paclitaxel in the central part and are restricted by albumin are not effective for transferring hydrophobic molecules in breast cancer. Some studies reveal that paclitaxel contained in albumin-encapsulated nanoparticles has better tumor penetration power compared to conventional paclitaxel. Tamoxifen targeted delivery is performed in all grades of breast cancer. Tamoxifen is an anti-estrogenic and non-steroidal drug that is very hydrophobic.[1] The utilization of nanoparticles along with this drug enhances its permeability to the tumor tissue. Also, its toxic impact on healthy non-tumor tissue cells is low.[32]

Solid lipid nanoparticles

Among other nanoparticles that are used as carriers in the field of drug delivery are Solid Lipid Nanoparticles, which are abbreviated as SLN, and are used for drugs that have low solubility in water, including tamoxifen, which is utilized for chemotherapy of breast cancer, and also drugs that are unstable in biological systems are suitable.[7] The advantages of SIN systems include the potential to control the drug release, deliver the drug to the intended tissue, and the stability of the loaded drug and its low toxicity He pointed out the tissues of the body.[1]

This new nano-sized drug delivery system based on solid lipid particles (SL) was introduced in 1992.[33] The lipid matrix of this drug delivery system is made of natural lipids that can be easily decomposed in the human body. Also, this system has been stable in terms of physical characteristics (size, electric charge, and morphology) for one year. Recently, tamoxifen was encapsulated in SLN (solid lipid nanoparticles) by high-pressure homogenization.[34] In this method, SLN is first prepared and then the drug is encapsulated in it. The main ingredients in making SLN include solid lipid emulsifier and water. In this way, a mixture of hydrogenated palm oil and hydrogenated soybean oil lecithin is heated at a temperature of 65 to 70 degrees Celsius to obtain a yellow lipid solution. Then a solution containing oleyl alcohol, thimerosal, sorbitol, and double distilled water is added to the obtained lipid solution, and then using a homogenizer and a high-pressure homogenizer, tamoxifen dissolved in oleyl alcohol with pre-emulsion The SLN is mixed using a homogenizer, thus tamoxifen is entrapped in the molten lipid. In this type of drug delivery system, there is no need for organic solvents and they can be produced in large quantities.[35]

Gene therapy

The strategy in gene therapy includes the transfer of tumor suppressor genes and suicide genes, increasing the immunological response of bone marrow preservation by using drug-resistant genes.[36] Gene therapy is useful for the mutation or amplification of multiple genes. Nanoparticle-assisted DNA and RNA delivery systems are useful for gene transfer to a variety of cancers, including breast cancer.[37] Combining tumor cells with iRNA is a technology based on its inactivation and has many clinical applications. Inhibition of breast cancer oncogenes leads to apoptosis induction and increased sensitivity to breast cancer cells chemotherapy. The uptake and stability of siRNA by cells are rectified by their absorption in nanoparticles.[6]

Considering that the utilization of conventional tumor imaging and detection methods has limitations and disadvantages, the utilization of nanotechnologies including aptamers, nanobodies, and quantum nanoparticles can be a new strategy for the early detection of cancer, specifically breast cancer.

Apart from cancer assessment, aptamers are also utilized in treatment. The technology of aptamer has been extended as an effective and valid technology and some studies have been conducted on aptamer users, today aptamers are utilized in different aspects as therapeutic, and diagnostic tools in the expansion of drug delivery systems. However, aptamers still find their place in medical treatment and diagnosis. Nanoparticles connected with antibodies can be utilized in the simultaneous identification of multiple molecular targets in fragments of small tumors. In addition, considering the anticancer drugs' side effects, it seems essential to utilize safe drug delivery systems with biocompatibility, such as liposomes and solid lipid nanoparticles, which deliver the drug to the intended tissue with high exclusivity. This method's basis is to reach enough amounts of medicine to the tumor place for a certain period and decrease the detrimental impact of the medicine on other organs.

The system of Solid lipid nanoparticles is complex with unique benefits and harms that make it different from other cloned systems. More studies by nuclear magnetic resonance methods are necessary to clarify the mechanism of drug delivery by this system. Limited information is available on the aptamer's toxicity. Thus, to perform aptamer therapy, it is essential to know their toxicity level. The main problem in cancer chemotherapy is the undesirable side effects of drugs. A single dose or a short period of use of these drugs can pose serious dangers to human health, but the use of biodegradable particles in Nano size for a long time or even a treatment period can cause undesirable harmful impacts. Thus, there are still limitations and challenges to the use of nanoparticles in medicine. It is hoped that shortly the synthesis costs will be reduced and the pharmacokinetic attributes will increase so that the nanoparticle's productivity will increase and overcome their use limitations.

Conclusion

In the current study, the benefits of nanoparticles and their applications in breast cancer treatment and diagnosis were discussed. Nanoparticles can be utilized in medicine in the fields of treatment and diagnosis of diseases, drug delivery, and biological imaging. The nanotechnology advancement in oncology will provide special possibilities to detect multiple molecular targets simultaneously in small tumor samples to adopt a treatment strategy. The use of nanoparticles in tumor imaging is progressing rapidly and will make it possible to simultaneously identify and target cancer-related antigens. Shortly, nanotechnology will create an important revolution not only in oncology but in all stages of medical science.

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Conflict of interest

None.

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Ethics statement

None.

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