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Research Article

A new approach to breast cancer therapy: targeted nanocarrier systems

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ABSTRACT

Cancer is one of the most prevalent diseases in the world. Breast cancer is the second most deadly cancer type after lung cancer. Surgical intervention, chemotherapy, and radiotherapy are the most used conventional methods in the treatment of breast cancer. The non-targeted approach of conventional treatments causes serious side effects in healthy cells and tissues, and often mortality is due to the side effects of these conventional treatments. In recent years, nano-sized particles called drug delivery systems targeting cancer cells have attracted attention as a new approach to cancer treatment. The fact that these nanocarrier systems target tumor cells without damaging healthy tissues has been a hope for breast cancer. Moreover, nanocarriers are unique biomaterials that may exhibit low toxicity, high biocompatibility, biodegradability, ease of use, high dose drug loading, and adjustable surface functionalities. In the present study, we summarize recent studies of nanocarriers that offer a critical review of an alternative strategy to breast cancer therapy.

Keywords: Drug delivery systems, breast cancer, nanocarriers, nanoparticles.

Meme kanseri tedavisinde yeni bir yaklaşım: hedefe özgü nanotaşıyıcı sistemler

ÖZ

Kanser, dünyadaki en yaygın hastalıklardan biridir. Meme kanseri, akciğer kanserinden sonra ikinci en ölümcül kanser türüdür. Cerrahi müdahale, kemoterapi ve radyoterapi meme kanseri tedavisinde en çok kullanılan geleneksel yöntemlerdir. Konvansiyonel tedavilerin hedefe yönelik olmayan yaklaşımı, sağlıklı hücrelerde ve dokularda ciddi yan etkilere neden olur ve mortalite genellikle bu geleneksel tedavilerin yan etkilerinden dolayı gerçekleşmektedir. Son yıllarda kanser hücrelerini hedef alan ilaç taşıyıcı sistemler adı verilen nano boyutlu partiküller kanser tedavisinde yeni bir yaklaşım olarak dikkatleri üzerine çekmektedir. Bu nanotaşıyıcı sistemlerin sağlıklı dokulara zarar vermeden tümör hücrelerini hedef alması meme kanseri tedavisi için umut verici bir yaklaşımdır. Ayrıca nanotaşıyıcılar, düşük toksisite, yüksek biyouyumluluk, biyobozunurluk, kullanım kolaylığı, yüksek doz ilaç yükleme ve ayarlanabilir yüzey işlevleri gösterebilen benzersiz biyomalzemelerdir. Bu çalışmada, meme kanseri tedavisine alternatif bir yaklaşım sunan nanotaşıyıcıların son çalışmalarını eleştirel bir analizle özetledik.

Anahtar Kelimeler: İlaç taşıyıcı sistemler, meme kanseri, nanotaşıyıcılar, nanopartiküller.

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1. INTRODUCTION

Cancer is a complicated disease resulting from the uncontrolled division and proliferation of malignant cells under the influence of genetic and environmental factors, potentially spreading to or invading various parts of the body. The World Health Organization estimates 18 million new cancer cases worldwide in 2018, and 10 million cancer deaths are expected. It is estimated that the number of new cases will be 29-37 million, nearly double the global burden for 2040.

Lung cancer is the most diagnosed cancer type (11.6%) and has the highest mortality rate, followed by breast cancer (11.6%), mostly seen in women, followed by colorectal cancer (10%). Relative to both sexes, the incidence of breast cancer, the second most common cancer, is only 1% in men (Figure 1). The survival rate of breast cancer, which has a higher incidence in women, depends on early diagnosis, and it is estimated that this rate will be 5 years after the diagnosis in advanced breast cancer cases, in the light of research.[1]

Age, gender, hormone therapy[2], environmental conditions, hereditary variables, and consuming habits[3–5] are all risk factors for the development and spread of breast cancer. Breast cancer incidence increases with age, it is less common in developed than in developing countries,[5] and the risk are higher in people who consume alcohol[6] and cigarettes, considering their consumption habits. Some studies reveal a link between hormone therapy and an increased risk of breast cancer. Therefore, hormone therapy has a higher possibility of having breast cancer. Statistical data show that the survival rate is still below 25 percent in the last 5 years of breast cancer treatment.[4,7]

Surgical intervention, chemotherapy, and radiotherapy, the so-called conventional methods of treatment, or a combination of these methods have been preferred for many years in the treatment of breast cancer. Surgical resection, i.e., removal of the entire breast to remove the tumor, is stressful for the patient both physically (due to the loss of the existing organ or tissue) and psychologically and aesthetically. Chemotherapeutic agents used in conventional chemotherapy cause controlled death of rapidly growing and proliferating cancer cells through different pathway mechanisms, including the destruction of the cell membrane, damage to cell integrity, inhibition of DNA synthesis, and impairment of mitosis.[8] The main disadvantage of the agents used in chemotherapy is that they have toxic effects on healthy cells and tissues due to their non-selectivity. They can also cause unexpected and undesirable negative side effects such as nausea and loss of appetite.[9] Serious side effects of chemotherapeutic drugs on healthy tissues and organs increase the death rate in cancer. Because of the low absorption of these medications at the tumor site, greater doses are required, resulting in increased toxicity and multidrug resistance in normal healthy tissues and cells. As a result, it is preferable to create chemotherapeutic drugs that target cancer cells to minimize adverse side effects.[9]

Over the past two decades, work in nanotechnology has profoundly impacted clinical therapeutics in general. Nanoscale drug delivery systems have the potential to solve some of these issues by reducing toxicity in normal cells and increasing therapeutic efficacy due to features such as active cellular uptake, increased permeability, and retention effect.[10] Cancer chemoresistance is a phenomenon that occurs when cancer cells that were originally inhibited by an anticancer agent develop resistance to that drug after some time. Therefore, there is a need for new, more targeted drugs to prevent cancer development, suppress side effects, and relieve pain caused by chemotherapy.[11]

Nanocarriers (NCs) or drug carriers are currently being prepared from organic and inorganic compounds, proteins, lipids, and synthetic polymers for the improvement of cancer therapeutics. When compared to direct delivery of chemotherapeutic drugs, medication encapsulation in a carrier has various advantages, such as circulatory disruption protection, improved drug solubility, increased drug stability, targeted drug delivery, and reduced toxic side effects.[12] Liposomes, mesoporous silica NCs, viral NCs, polymer-, metal-, or carbon-based NCs have been explored in breast cancer therapy to date.[13,14] Various techniques such as encapsulation, covalent or electrostatic bonding, and adsorption are used to load drugs into NCs, again depending on the NCs.[15] NCs enable easy transport of poorly soluble, hydrophobic drugs in the blood and make cancer therapeutics biocompatible.[16] At the same time, they are nanoscale particles that enable slow release of the drug, target cancer cells, increase permeability, and are nontoxic and biodegradable.[17]

In in vitro breast cancer studies, many targeted NC systems were investigated using breast cancer cell lines with different characteristics.[18] At the same time, doxorubicin (Dox), which is highly chosen in the treatment of many cancers, has been widely used as a reference agent and therapeutic agent in drug delivery systems. The other chemotherapeutics (trastuzumab, cisplatin, paclitaxel (PTX), carboplatin, anastrozole, fulvestrant, etc.) have been studied in phase 2 phase 3 clinical trials. In addition, combination studies have investigated the synergistic effects of these chemotherapeutic agents against breast cancer when used together.[19–23]

Concentrations of drugs used in the treatment of breast cancer without the use of a drug delivery system require pharmacologically higher doses than concentrations of

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drugs loaded into targeted drug delivery systems. The usage of targeted drug carriers could greatly reduce the side effects and serious damages caused by non-targeted chemotherapeutic drugs in healthy cells and tissues. Therefore, combination therapy and NCs have the potential to reduce damage to healthy tissue and cells. NCs are also important in combination therapies, where different drugs are used together, or in treatments that use oligonucleotides, as they respond to the need to transport drugs to the target without degradation.[24]

2. BIOMARKERS

A biomarker is a valuable tool for disease diagnosis and treatment in the clinic. Cancer cells are targeted by utilizing molecular recognition markers in breast cancer treatment. The use of biomarkers to target drug delivery can increase the target specificity of therapies for cancer cells by reducing toxicity to healthy cells. Moreover, several biomarkers have been linked to the beginning and progression of BC. Progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor (HER2/ERBB2) are the most common BC biomarkers. While ER overexpression is found in most breast tumors, HER2 overexpression is found in about a quarter of them.[25] Triple-negative breast cancer (TNBC) is a tumor that does not express ER, PR, or HER2.[26,27] As a result, these biomarkers have been used in the classification of BC and the development of novel treatments based on target ligands.

2.1. HER 2

HER2 is a transmembrane glycogen protein with three distinct regions. HER1, HER2, HER3, and HER4 are the four proteins that constitute the HER family. HER2 is the only receptor without a known ligand, yet it aids cell proliferation by dimerizing with three other members of the family.[28] N-terminal extracellular domain, which is separated into subdomains, makes up the majority of HER2 (I-IV). Homo-dimerization and heterodimerization are controlled by cysteine-rich subdomains II and IV.[28] Subdomain II's dimerization arm emits dimerization. Pertuzumab and trastuzumab, both monoclonal antibodies, have been found as dimerization inhibitors. They attach to HER2's dimerization arm and inhibit signaling, preventing dimerization with other family members, which slows cell proliferation.[29]

2.2. ER

ERs can be found both intracellularly and in the membrane of BC cells. Most breast tumors are ER+, and ER+ type BC can affect both premenopausal and postmenopausal women. For ER+ breast cancers, tamoxifen is the most prescribed antagonist. Tamoxifen does not directly target adipose tissues, so targeted drug release of NPs is critical.[30] Dreaden et al. revealed the delivery of tamoxifen-conjugated NPs to ERs.[31] The nanoparticles increased the efficacy of tamoxifen 2.7 times compared to the free drug. Li and colleagues demonstrated a polymer-based NP-based tamoxifen delivery system into ER+ BC cells with dramatically lower cytotoxicity than healthy cells.[32]

2.3. PR

PR is a steroid hormone receptor that mediates progesterone. PR plays a role in lobuloalveolar differentiation.[33] They are used in clinical practice to identify patients with invasive BC who may benefit from various types of endocrine therapy. It is employed as a predictor for all therapy phases, including adjuvant and neoadjuvant.[34]

2.4. TNBC

Targeted drug delivery is more difficult because 15% of breast cancers lack ER, PR, or HER2. 2. Although basal type cancers account for 85 percent of TNBC, not all basal type tumors are triple-negative. TNBC-like tumors with no ER, PR, or HER2 expression are known as basal-type cancers.[35] However, specific protein alterations may occur in basal-type cancers not seen in TNBC. Many solid tumors, including breast cancer, express folic acid, transferrin, arginylglycylase particulate acid (RGD), and epidermal growth factor receptors (EGFR). Wu et al. devised a drug delivery system mediated by RGD ligand-conjugated NPs that exhibited better cellular absorption in MDA-MB-231 cells than the untargeted system.[36] Furthermore, treating TNBC with a combination of therapeutic drugs at the same time has been demonstrated to be more effective. Both in vitro and in vivo, the approach has shown effectiveness in suppressing cell growth.[37,38]

3. TARGETING LIGANDS FOR BREAST CANCER THERAPY

For active targeting of breast cancer cells, various approaches and techniques are currently available monoclonal antibodies were previously used to target cell surface epitopes. The number of possible ligands for targeted BC therapy has significantly increased due to additional research and comprehensive screening of peptide and aptamer archives.[39] Antibodies, peptides, aptamers, oligosaccharides, and small molecules are among the ligands now in use.[40–43] This new targeting strategy includes a form of chemical recognition that triggers the binding of ligand receptors. The NPs can be selectively fixed to the tumor cell's surface thanks to this conjugation.

Previous research has also demonstrated this potential binding and the efficacy of these NPs in vitro and in vivo.[44–46] For example, when NPs connect to a targeted

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ligand, they often internalize more quickly and undergo receptor-mediated endocytosis.[47,48] The binding affinity of the ligand is raised because of definite conjugation, resulting in more effective receptor-mediated endocytosis. Monoclonal antibodies conjugated with complete NP families like superparamagnetic iron oxide nanoparticles[49] quantum dots,[50] and liposomes[51] have been used in numerous investigations to contribute to BC-specific targeting.

Monoclonal antibodies regulate redundant parts of single-chain variable segments via bioengineering, lowering size and immunogenicity compared to the original antibody. This modified T cell with a chimeric antigen receptor is a promising approach applied to the therapy of various malignancies, such as B-cell leukemia and lymphoma[52] Aptamers and peptides are two more notable ligands, both of which are characterized by practical targeting approaches[53,54].

4. NANOCARRIERS SYSTEMS in BREAST CANCER

Nanoparticles (NPs) are small particles with sizes between 1-100 nm. Although NPs in drug delivery systems are not yet widely employed in clinical treatments, various research studies are underway to explore the potential benefits of NPs in drug delivery systems for cancer treatment. Because of their biocompatibility, water dispersion, and biodegradability, NPs have become popular as nanocarriers. The use of nanoparticles in cancer therapy increases drug solubility and half-life, boosting the bioavailability of many chemotherapy medicines.[55] Furthermore, through improved permeability and retention (EPR), NPs might increase medication accumulation in cancer tissues.[56] Furthermore, by targeting particular cancer sites with target ligands and decreasing side effects, the NPs-anti-cancer drug combination can improve therapeutic efficacy.[57,58] NPs are employed in the BC targeted drug delivery system in various ways. Polymer, liposomal, carbon, metal, protein-based, and mesoporous silica NPs are some of the available NPs (Figure 2).

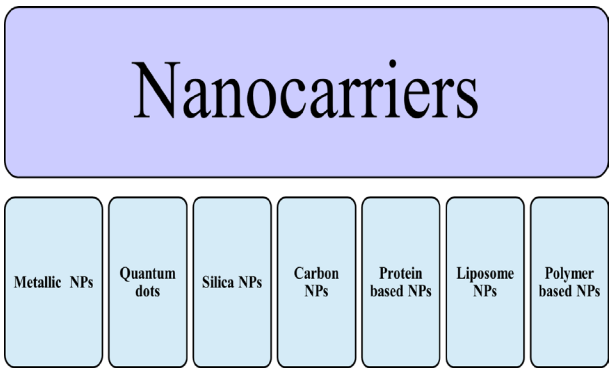

Figure 2. Types of nanocarriers for treatments of breast cancer

4.1. Metallic Nanoparticles

Researchers are interested in metal or metal oxide-based nanoparticles because of their potential applications in cancer diagnostics and treatment.[59] Photodynamic therapy (PDT), photothermal therapy (PTT), immunotherapy, and chemotherapy are cancer treatment techniques that use metallic nanoparticles.[60] Because of their magnetic, optical, thermal, and electrical capabilities, metallic nanoparticles have many applications in cancer therapy and detection. Metallic nanoparticles (NPs), including Au, Ag, Pt, Zn, and TiO, show promise for anticancer treatments and diagnostics. Magnetic nanoparticles (MNPs), such as gold nanoparticles (AuNPs) and Fe_3O_4, show promise in anticancer therapy and diagnostic imaging of breast cancers.[61,62]

Several metal-based nanoparticles use chemical processes to induce intracellular ROS production, oxidative stress, and tumor cell apoptosis.[63] Silver nanoparticles (AgNPs) have anti-proliferative, pro-apoptotic, and anti-angiogenic action on cancer cells.[64] ZnO nanoparticles can modify the micronucleus within tumor cells, speeding mitotic and interphase apoptotic cell death, acting as genotoxic medicines for anticancer therapy.[65] Nanoparticles of CuO, Fe_2O_3, silica, CeO_2, and TiO2 have been studied in the diagnosis and therapy of BC.[66] Through a DNA-damage mechanism, CeO_2 nanoparticles induce apoptotic cell death and oxidative stress.[67]

The remarkable properties of gold nanoparticles make them worthy of investigation. These nanoparticles' size, shape, and surface activity can be easily adjusted to improve circulation time, targeting ability, biocompatibility, and tumor cell attraction.[68] To enable active targeting, gold nanoparticles are typically coated with organic compounds.[69] In various investigations, gold nanoparticles targeting EGFR were found to inhibit breast cancer cells. Surface conjugation considerably stabilizes gold nanoparticles compared to unconjugated nanoparticles.

Kardani et al. prepared gold nanoparticles loaded with anti-miR-155 and examined their activity on the MCF-7 cell line. To facilitate tumor-targeted dispersion, the nanoparticles were modified with the AS1411 aptamer, which binds to the nucleus of cancer cells. Zhao et al. used positron emission tomography (PET) to detect primary cancer cells and lung metastases in a mouse with breast cancer.[70] The primary disadvantage of employing gold nanoparticles is their low biodegradability.

The magnetic core of magnetic iron oxide nanoparticles is maghemite (Fe_2O_3) or magnetite (Fe_3O_4). Maghemite, rather than magnetite, is recommended as the core material for magnetic nanoparticles because the Fe (III)

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released from maghemite is less hazardous than the Fe (II) emitted from magnetite.[71] Due to the hydrophobicity of these nanoparticles, direct use causes them to aggregate in the plasma. Coating the magnetic core with a hydrophilic material can help overcome this disadvantage. PEG, polysaccharides, PLA, and dextran are biopolymers that can be employed as coating materials.[72,73] Hyperthermia is a treatment method in which heat reduces tumor growth. Because tumor cells are heat sensitive, magnetic hyperthermia employing superparamagnetic iron oxide nanoparticles (SPIONS) can reduce tumor size.[74]

To increase the stability of iron oxide nanoparticles, PEG is often coated on them. Furthermore, functional groups on the surface of PEG-coated nanoparticles facilitate ligand conjugation. The drug can be loaded by sticking to the surface or sealing it within the core. There are various studies in the literature on nanoparticles of iron oxide for targeted treatment. Jeon et al. produced paclitaxel-loaded SPIONs and coated the nanoparticles' surfaces with folic acid (FA). FA conjugation increased nanoparticle absorption by tumor cells.[75] Methotrexate-conjugated arginine functionalized magnetic nanoparticles and their targeting abilities were investigated by Attari et al. These nanoparticles effectively delivered the drug to the tumor site.[76] Soleimani et al. produced a folate-conjugated iron oxide nanoparticle technology and examined its targetability.[77]

4.2. Quantum Dots

Quantum dots (QDs) are semiconductors that are widely used in cancer imaging and range in size from 2 to 10 nm[78]. They are very promising for cancer imaging due to their high surface/volume ratio, resistance to photobleaching, high brightness, and tunable optics. PEGylation is commonly performed on QDs to increase water solubility and reduce RES formation.[79] QDs emitting multiple wavelengths have been studied in breast cancer. This study combined QDs with complementary antibodies to detect quantitative biomarkers such as EGFR, ER, HER2, and PR.[80] QDs have two significant disadvantages; the first is that they contain heavy metals that are hazardous to our bodies in their inner core. The second is the hydrophobicity of metallic QDs and their difficulties in using them in vivo. Researchers have recently turned to studies on carbon-based QDs in cancer therapy. It was shown that carbon QDs synthesized by conjugating quinic acid as a targeting agent and loading it with Gemcitabine charge have good light properties and can be used as theranostic agents.[81] Graphene quantum dots (GQDs) are used in photodynamic therapy (PDT). PDT is a non-invasive procedure that irradiates GQDs to inhibit tumor growth. Because conventional PDT drugs are bombarded with UV-Visible light, their use in deeper tissue malignancies is limited. Furthermore, GQDs are more efficient PDT agents because they can be irradiated at longer wavelengths.[82]

4.3. Silica Nanoparticles

Mesoporous silica nanoparticles have a porous surface and high drug loading capacity. Furthermore, researchers have chosen it for therapeutically targeted distribution due to its easily replaceable surface, the potential for pore size modification, and vast surface.[83] Tsai et al. discovered that anti-HER2 monoclonal antibodies linked to silica nanoparticles could be used to effectively target breast cancer cells. To target HER2-positive breast cancer cells, they coupled mesoporous silica nanoparticles with Herceptin. Nanoparticles with a high concentration of Herceptin were highly effective at targeting BT-474 cell lines. Internalization of Herceptin-conjugated nanoparticles in BT-474 cells has been demonstrated.[84] Meng et al. developed silica nanoparticles containing doxorubicin and siRNA coupled with PEI and PEG on their surface. According to the findings, there was improved permeability at the tumor location and decreased nanoparticle aggregation in the RES. It has also been discovered that a lower dosage of doxorubicin can be supplied using this nanoparticulate method, which helps to minimize doxorubicin's cardiovascular toxicity.[85] When it comes to toxicity and biocompatibility, mesoporous silica nanoparticles outperform metallic nanoparticles. However, their inability to penetrate the tumor mass is a significant disadvantage. In vitro targeting of mesoporous nanoparticles conjugated with Herceptin was investigated by Milgroom et al. As a result, researchers discovered that silica nanoparticles are biocompatible, stable, and excellent drug carriers. It has also been demonstrated that antibody-conjugated silica nanoparticles can stay in the bloodstream for an extended period, overcoming half-life difficulties.[86]

Fortuni et al. revealed doxorubicin-loaded mesoporous nanoparticles and coupled them with HA. The data indicated increased anti-tumor efficacy and anticancer cell selectivity.[87] In another study, PEG- and chitosan-functionalized mesoporous silica nanoparticles were employed to transport doxorubicin to the MCF-7 cell line. These nanoparticles revealed increased medicine effectiveness as well as drug loading and release capacities.[88]

4.4. Carbon Nanoparticles

Carbon nanoparticles such as fullerenes, nanotubes, and graphene are extensively employed in cancer therapy. Carbon nanoparticle features such as shape, size, structure, surface charge, aggregation, and chemical composition can influence how they interact with cells and biomolecules.[89] These nanoparticles were supposed to be superior to metal-based nanoparticles in terms of

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focused and regulated medication administration. Carbon nanotubes are long, hollow, cylindrical structures made of graphene sheet walls. Based on the number of graphene sheet coverings, the fullerene allotropes are classed as single-walled or multi-walled nanotubes. It is remarkable due to its chemical stability, tunable surfaces, and unique thermal and electrical properties.[90] HER2 immunoglobulin 'Y' conjugated nanotubes were used to identify and destroy tumors in an in vivo model of HER2-expressing breast cancer cells.[91] Drug loading into nanotubes can be accomplished in filament loading and direct surface loading.[92] Nanotubes have a lower drug loading capacity, but it has been discovered that employing copolymers on the surface can improve the loading capacity of tiny hydrophobic medicines.[93] However, for bulky pharmaceuticals, only a limited amount of space is accessible on the surface of the polymers, restricting drug loading and subsequent ligand conjugation.[94] Paclitaxel was combined with docosanol and then conjugated to the surface of nanotubes by Shao et al. In addition, in the same study, folic acid was conjugated to the surface of nanotubes to target breast cancer tissue and increase treatment efficacy.[95] Carbon-based nanoparticles can be used effectively in the targeted release of drugs in cancer.[96] Docetaxel-loaded fullerene was found to have 4.2-fold higher bioavailability than free drug and enhanced cytotoxicity in breast cancer cells.[97]

Carbon nanoparticles have recently been studied for their potential usefulness in photodynamic treatment. Carbon nanoparticles can aggregate late at the tumor site and absorb infrared radiation, generating heat and cytotoxicity.[96] Carbon nanoparticles are substantially less soluble in aqueous media, causing agglomeration in biological fluids, and they are highly resistant to enzymatic oxidation because they are not removed from the body.[98]

4.5. Protein-Based NPs

Protein-based NPs are a group of viral NPs that resemble viruses' protein envelopes or capsids. In the absence of the virus genome, these viral NPs are not contagious. In the production of viral NPs, plant tissues can be used, and recombinant proteins produced in plants can then be commercially increased to appropriate production levels.[99] The surface of viral NPs is suitable for drug conjugation and is emerging as a highly favorable method for targeted drug delivery. For example, trastuzumab is carried by viral NPs as a targeted therapy in patients with HER2+ cancer. Esfandiari et al. potato virus X (PVX) has been identified and reported to cause increased mortality of BC cells. Esfandiari et al. achieved selective targeting of BC by combining PVX with the trastuzumab monoclonal antibody that can suppress proliferation and signal transduction of BC cells.[100] Le et al. revealed that PVX-Dox treatment of MDA-MB-231 BC xenografts in athymic mice resulted in reduced tumor growth.[101] In a murine BC model, glycophosphatidylinositol and HER2 antigen conjugated to influenza virus NPs and HER2-expressing inhibited tumor growth.[102] Viral NPs are evolving, and viral NPs are predicted to play an important clinical role very soon.

4.6. Liposome-Based NPs

Liposomal NPs (LNPs) are spherical vesicles that contain one or more phospholipid bilayers and can reach diameters of several hundred nanometers. LNPs consist of a hydrophilic inner core and a hydrophobic layer covering that. The unique morphology of LNPs makes them important for the delivery of hydrophobic medicine. LNPs are one of the most favored drug carrier systems that allow hydrophobic agents to be encapsulated in the outer layer while simultaneously encapsulating hydrophilic agents in the inner core. In this way, they also reduce the side effects of drugs that are not targeted in the body. Encapsulation of a drug can greatly reduce its toxicity, as it greatly inhibits its release until it reaches the target. Several studies have shown that some chemotherapeutic drugs, such as DOX and Vincristine[103], were encapsulated in the inner core of LNPs, reducing their cardio cytotoxicity [104]. The efficacy of the PTX agent encapsulated with LNPs and the efficacy of these encapsulated forms on breast cancer cell lines were studied by Marcial et al.[105]

LNPs tend to infiltrate and accumulate in the bilayer of the tumor cell membrane. Pegylation of LNPs renders them with longer half-lives and higher target activity.[106] As carrier systems in passive targeting, pegylated LNPs have shown effective targeting both in vitro and in vivo. Wong and Chiu encapsulated vincristine and quercetin into the pegylated liposome. It showed prolonged plasma residence time and controlled release in vivo by pegylation. Also, compared to the two drugs, liposomal encapsulation has been shown to be the more effective approach.[107,108]

LNPs have been recognized as important carriers in the siRNA, peptide, and oligonucleotide-based gene therapy approach. Encapsulation of genetic material such as siRNA and peptides, which are rapidly degradable in the vascular environment, with LNPs protects them from degradation and allows them to be targeted using surface ligands.[109,110] LNPs, surface modified with A7R-cysteine peptide, were designed by Cao et al. as carrier systems for PTX delivery and tested in vitro and in vivo. In this study, increased cytotoxicity and accumulation were reported in BC xenografts, as more modified LNPs were vesiculated by BC cells due to the A7R-cysteine peptide; These results put frothed the importance of the peptide as a targeting ligand in the PTX-loaded targeted delivery system.[111] The novel drug delivery system produced by loading siRNA onto chitosan-coated LNPs was presented

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by Salva et al for the in vitro delivery of siRNA. This study provides evidence for the theory that co-administration of siHIF1-a (hypoxia-inducible factors) and siVEGF (vascular endothelial growth factors) will produce lower cytotoxicity and higher silencing efficiency. When the expressions of the relevant mRNAs were examined, it was reported that the proliferation of MCF-7 and MDA-MB-435 BC cells was significantly inhibited. In addition, stability analysis indicated that overnight serum treatment reported that chitosan-coated LNPs were able to protect siRNAs from serum degradation.[112] A bio-nanocarrier produced with the antigen located on the surface of hepatitis B virus and liposomes was loaded with siRNA to deliver HER2-expressing BC. This system successfully realized the gene silencing and protein knockdown through.[113] In this study, in which siRNA and a chemotherapeutic agent, Dox, were used together to overcome BC's multi-drug resistance (MDRChen et al. described a liposomal approach that used cationic and anionic liposomes in conjunction with polycation-DNA (LPD). A new capsule was produced to encapsulate both agents with this technique. Cellular uptake of Dox has been observed to be increased when combined with siVEGF in targeted passive metastatic BC. It has been observed that the entrapment efficiency of Dox was higher in anionic-LPD NCs through modification to overcome Pgp-mediated drug efflux.[114] Consequently, LNPs, one of the nanocarriers that have been needed for easily biodegradable therapeutic agents, especially peptides and siRNAs, to reach target cells without degradation, have become very popular. Also, LNPs have been often coated with polymers for better biocompatibility but this coating makes increases their size. Depending on the polymer used in the coating, the drug release process may also vary.

4.7. Polymer-Based NPs

Polymer-based nanoparticles (PNPs) are nanometer-sized colloidal nanoparticles. Typically, these NPs are created by attaching one copolymer to another polymer matrix.[115] Polymer-based nanocarriers can be produced from natural polymers such as cellulose and chitosan or synthetic polymers, which are more demanding in the biotechnological field with high biocompatibility.[116] Common techniques used in the chemical synthesis of PNPs are nanoprecipitation, emulsification, and salting. These chemical methods can be modified so that PNPs are specific to the drug they will carry, target to be transported, and lipophilicity, charge, and biocompatibility. Drugs can be carried by adsorbing to the surface of PNPs, forming chemical conjugation with PNPs, or loading into the core for active or passive delivery to the target site. PNPs have been a solution and advantage for hydrophobic anticancer agents.[117] The high solubility and permeability of PNPs facilitate the delivery of hydrophobic drugs in vivo, making them soluble. In addition to solubility, it also provides controlled release and long-term stability of the drug, thereby freeing the hydrophobic drug from its handicaps.[118] In addition, an extra coating on PNPs, PEG-phospholipid, has been reported to reduce toxicity by increasing the encapsulation efficiency of the drug.[119] PNPs have become important drug delivery systems for combination studies such as DOX and PTX or trastuzumab and cis-platin where anti-cancer agents are used together, and there are many studies in the literature on this subject.[120] NPs produced using poly(ε-caprolactone) have been reported to be targeted in breast cancer by loading tamoxifen into their PEG-modified and non-PEG-modified forms. Poly(ε-caprolactone) NCs modified with PEG demonstrated higher accumulation in breast cancer cells compared to the unmodified forms.[121,122] In addition, different studies have been presented in which not only chemotherapeutic agents but also photosensitizers have been preferred for cancer treatment. Photodynamic therapy using PNPs for the treatment of triple-negative breast cancer was reported by Jin et al.[123] In this study, it was revealed that PNPs conjugated with a luminescent substance when irradiated with light, produce ROS and lead to cell inhibition. PNPs conjugated with a cyclic arginine-glycine-aspartic acid peptide-modified photosensitizer showed negligible cytotoxicity but this conjugate could decrease the viability of the αvβ3 integrin-overexpressing MDA-MB-231 cells. In another study, passively targeting tumor cells by loading tamoxifen into PNPs produced from PLGA, an FDA-approved, biocompatible polymer, tumor cells demonstrated an enhanced cleavage of their DNA. Tamoxifen-loaded PLGA nanocarriers applied to MDA-MB-231 cell lines exhibited higher cytotoxicity and greater bioavailability than tamoxifen administered in free form.[124] For the treatment of TNBC, the synthesis of layer-by-layer NCs loaded with a combination of siRNA and Dox, with a controlled release approach, was improved by Deng et al. It was revealed that the increase in the layers of poly-L-Arginine (PLA) PNPs synthesized using the layer-by-layer technique both increased their size to 140 nm and enabled them to achieve a high loading capacity. In addition, PNPs co-loaded with siRNA and Dox and targeting the multidrug-resistant protein 1 (MRP1) drug efflux pump exhibited very high drug efficacy in animal models of TNBC.[19] Alongside LNPs, polymer-based drug delivery systems emerge as a different approach for delivering combined drugs to the target. Although the synthetic polymers used in the production of PNPs could be modified using different methods to respond to needs, their size continues to be around several hundred nanometers, which is higher than LNPs, this physical character affecting their biodistribution.[125]

In addition, nanofibers, which are among the biomaterials produced from synthetic or natural polymers, are one of the PNC groups developed for many different application areas such as drug delivery systems

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or cosmetics. Biocompatible polymers such as chitosan, PVA, PLA, and PEG, which have been widely preferred in drug delivery systems have been used in the synthesis of nanofibers.[126] The mechanical properties (elasticity and tensile strength) of nanofibers with a very large surface area/volume ratio also have exhibited the desired quality. Techniques to produce nanofibers from synthetic polymers: template synthesis, drawing, phase separation, electrospinning, and self-assembly.[127] Jayakumar et al., for example, employed the electrospinning process to create chitin and chitosan nanofibers.[128] In another study by Marty et al.,[129] nanofibers were fabricated as a drug delivery system to evaluate cell motility in metastatic breast cancer patients. Although nanofibers are a new approach as drug carriers, they have significant disadvantages such as their low drug loading capacity and toxic effects.

5. CONCLUSION

Cancer is a deadly disease that affects the whole world, and the number of cancer research projects is increasing. Breast cancer is one of the deadliest tumors, and typical breast cancer treatments include surgery, chemotherapy, and radiotherapy. Conventional therapy's lack of selectivity and targeting resulted in drug resistance and adverse effects that limited practical uses. In this context, targeted nanoparticles emerge as promising cancer treatment candidates. In this review, targeted nanocarrier systems that have the potential to be used in breast cancer treatment are emphasized. In various in vitro and in vivo studies on breast cancer, researchers have modified nanocarrier drug delivery systems with ligands specific to the receptors overexpressed at the tumor site to target cancer cells. These nanoparticle systems improve targeted and efficient drug delivery, provide slow and controlled drug release, reduce side effects, and reverse multidrug resistance. With the development of target-specific nanocarrier systems, the introduction of new materials, and the increased focus on breast cancer research, the value of targeted nanocarrier systems in breast cancer treatment will increase.

Conflict of interest

Authors declare that there is no a conflict of interest with any person, institute, company, etc.

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