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New developments in the nanocarrier-based drug delivery system for the treatment of breast cancer

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Abstract

Worldwide, breast cancer remains the leading cause of disease and mortality for women. Because of its aggressive nature and resistance to conventional medicines, triple negative breast cancer (TNBC) is very challenging to treat. Through focused tactics, recent advancements in nanocarrier technology have demonstrated promise in improving medication delivery, optimizing bioavailability, and raising drug concentrations at tumor locations. Nanoparticles have become a very useful tool for studying the imaging, diagnosis, and targeting of breast cancer. Their advanced physicochemical properties contribute to prolonged circulation in the bloodstream, as well as more efficient targeting of tumor cells. The accuracy with which nanoparticles can target tumors is improved by both passive targeting which takes advantage of characteristics like leaky vasculature, the tumor microenvironment, or direct application and active targeting which makes use of receptor-specific antibodies. By enhancing their ability to target cancer cells, nanoparticles provide an advantage over conventional medication formulations in that they can lessen the cytotoxic effects of anticancer drugs. Numerous formulations based on nanoparticles exist at different phases of preclinical and clinical development; the most extensively investigated include polymeric drug micelles, liposomes, dendrimers, carbon nanotubes, and nanorods. Polymeric nanoparticles and liposomes have been the most popular drug delivery vehicles for cancer therapy during the last ten years. Ongoing studies have, however, shown a number of these carriers' drawbacks. Consequently, there has been interest in hybrid nanoparticles, which combine the advantages of liposomes with polymeric nanoparticles. An overview of the most recent developments in the field of drug delivery using polymeric nanoparticles is given in this study. It also stresses the need of early identification in enhancing patient outcomes and the potential of nanocarriers to transform BC treatment.

Key words breast cancer, nanomaterials, nanoparticles, liposomes, drug delivery system

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Introduction

It has long been observed that the clinical use of many effective drugs for cancer and other diseases is limited due to several factors: 1) poor water solubility, which leads to low systemic bioavailability [1]. During treatment, patients often require large volumes of saline, which can lead to water intoxication [2]. 2) Instability in vivo—drugs are dispersed throughout the body, making them prone to metabolism and elimination, which alters drug concentration and reduces efficacy [3]. 3) Toxic side effects—these drugs often have harmful effects on healthy cells, such as nephrotoxicity, neurovirulence, and gastrointestinal issues [4]. Patients may need to take additional protective medications, adding to their discomfort. As a result, high doses are not feasible, and the drug's effectiveness is compromised. 4) Drug resistance multidrug resistance can develop, diminishing the effectiveness of future treatments [5]. Therefore, there is an urgent need to develop new cancer therapies, improve drug absorption, and optimize drug delivery. Researchers have developed NPs, which are categorized in **Figure 1** to target and visualize metastatic BC.

Nanoparticles (NPs) are thought to be one of the possible delivery systems which could take care of clinical application issues. NPs can generally be defined as colloidal particles with a size range of 10-1000 nm [6]. They may increase target selectivity, stability, and bioavailability, thus augmenting therapeutic approaches. All these advantages lead to minimized side effects while taking care of the drawbacks of classical therapeutic approaches [7]. Additionally, by improving the pharmacokinetics of drugs, prolonging half-life, and increasing drug solubility [8]. NPs can advantage drug delivery. Unfortunately, NPs as a drug carrier system have more advantages than disadvantages. By solubilizing hydrophobic substances in an aqueous solution, they are able to increase the drug solubility, maintain its stability, and extend blood circulation time. Targeted delivery of the drug with NP further minimizes side effects and develops countermeasures for drug resistance. All things considered, NPs show stability in vivo and offer an effective way to deliver medications to the target region [9].

Because of their improved drug delivery and therapeutic effects on a variety of cancer types, drug-loaded NPs are currently thought to be very promising for effective cancer treatment [10]. Polymeric nanomedicines are another name for polymeric nanocarriers, which encapsulate or conjugate anticancer medications. These nanocarriers come in a variety of shapes, such as dendrimers, vesicles, micelles, nanospheres, nanogels, and polymer–drug conjugates [11]. Their capacity to specifically target tumor cells and co-deliver numerous therapeutic medicines is what is driving their increasing popularity [12]. These nanoparticle systems can transport a wide variety of therapeutic molecules, including cytotoxic medicines, small interference RNA (siRNA), chemosensitizers, and antiangiogenic agents [13]. The distinct pathophysiology of cancer cells causes NPs to increase permeability and the retention effect. Increased intracellular medication concentrations result from NPs building up inside tumor cells without P-glycoprotein recognizing them. With minimal harm to healthy peripheral tissues, this capability allows NPs to deliver chemotherapy directly to tumor cells at the ideal time, guaranteeing excellent efficacy [14]. In this context, a multitargeting system (MTS) has drawn a lot of interest. By adding several functional ligands to the NP surface that can bind to various cell surface receptors, this tactic improves the multivalent contacts between the NPs and the target cells, increasing cellular recognition and uptake. Drug efficacy is further enhanced by other strategies, such as adding pH-sensitive groups [15]. Numerous multifunctional NPs are being investigated as NPs continue to improve cancer therapy methods.

Human breast cancer

The mammary glands are the source of prostate cancer, which is frequently linked to breast tissue. About 7% of occurrences of BC occur in women under 40, and less than 4% occur in those under 35. BC is most frequently diagnosed in women. BC is comparatively uncommon among younger women [16]. The expression levels of important markers like progesterone receptor, estrogen receptor, and HER-2/neu (human epidermal growth factor receptor 2) are used to categorize the diverse subtypes of breast cancer, which represent a heterogeneous disease [17]. The development and spread of BC are significantly influenced by breast cancer stem cells (BCSCs). The development of a tumor mass with the capacity to replicate itself is facilitated by these stem cells' capacity to self-renew while also generating daughter cells. Although BCSCs only make up a minor portion of most tumors, in some malignancies, including melanoma, they can account for up to 25% of the overall mass [18]. Based on tumor size (T), involvement of lymph nodes (N), and metastasis (M), BC is divided into four stages by the TNM (Tumor, Node, Metastasis) classification.

One possible way to address issues related to BC is using nanotechnology. Numerous scientists are investigating different drug delivery methods based on nanotechnology and how they work to treat breast cancer. BC can be detected using a variety of nanoparticle forms, although the most widely used ones are carbon nanorods (e.g., gold nanorods [19]), nanowires (e.g., gold nanowires [20]), and nanobarcodes. In nanotechnology, semiconductor quantum dots (QDs) are an interesting new development. Compared to fluorescent proteins and chemical dyes, these nanoscale light-emitting particles have benefits. Semiconductor QDs are perfect for cellular and in vivo biomolecular imaging because of their special electrical and optical characteristics [21]. Yu et al. created blue light-emitting QDs based on cadmium oxide and selenium with a diameter of around 2 nanometers and red light-emitting QDs with a diameter of 7 nanometers [22]. High resolution and sensitivity have been established using combined optical and X-ray imaging, which enables the detection of both small, aberrant tumor daughter cells and big BC tumors. Chemotherapy NPs can be administered by active or passive routes. Through the use of biomarkers and probes based on NPs, nanotechnology also contributes to the diagnosis of molecular cancer. Individual NPs can be attached to several ligands, resulting in a multivalent effect that improves binding affinity and specificity, making them useful diagnostic tools.

Nanomaterials mechanism of action in reducing breast cancer medication resistance

For aggressive types of breast cancer, especially TNBC, chemotherapy is a commonly utilized treatment. Inhibiting drug efflux and inactivation [23], blocking alternative signaling pathways, focusing on DNA repair mechanisms, suppressing the epithelial-mesenchymal transition (EMT) process, and lowering CSC properties are some of the strategies that can be used to address the problem of drug resistance in breast cancer. In addition to aiding the transport of chemotherapeutic medications, improving angiogenesis, avoiding immune system reactions, and altering the tumor microenvironment, nanomaterials are also used to prevent tumor cell proliferation, invasion, and metastasis [24]. Nanomaterials are crucial for overcoming chemotherapy resistance, according to a number of studies. **Figure 2** summarizes the possible therapeutic pathways underlying BC resistance, emphasizing the prospective therapeutic options for the treatment of BC [25].

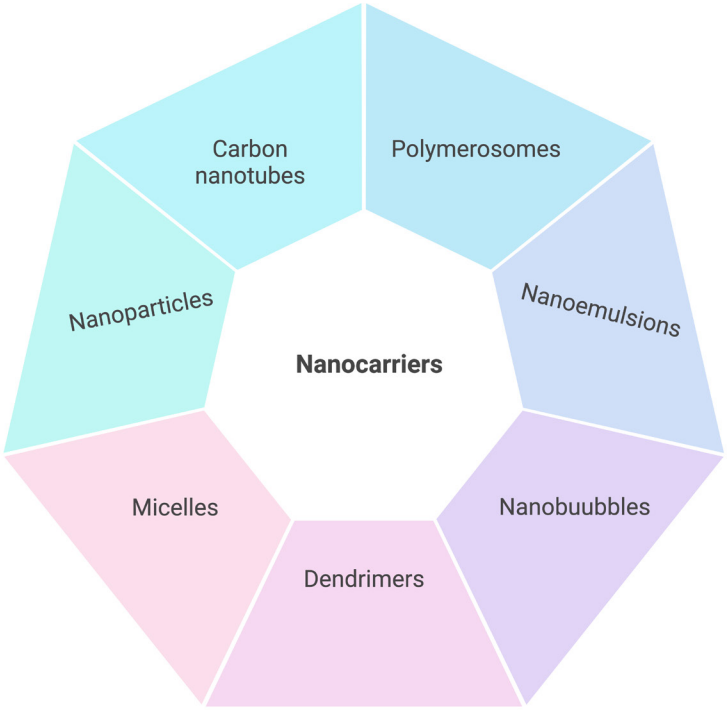

Figure 1. Different classifications of nanocarriers on the basis of structure and morphology.

Cytotoxic medications must be completely absorbed by cancer cells in order to treat the disease effectively. Overcoming chemotherapeutic resistance requires increasing medication absorption [26]. Drug efflux mediated by transmembrane pumps is one of the main mechanisms underlying treatment resistance. In order to overcome multidrug resistance to chemotherapeutic medications, researchers have created acid-grafted poly(b-amino ester) NPs for encapsulating cleavage protein B. In lower pH levels, the pH-sensitive releasing mechanism of these NPs improves drug release. Importantly, by blocking P-glycoprotein (P-gp) expression and interfering with the energy source for drug efflux, they can also reverse multidrug resistance, offering a novel approach to treating BC [27]. Based on star-shaped polyester (FA-TRI-CL), Guo's group created folic acid-modified NPs ((DOX + CUR)-FA-NPs) that efficiently target P-gp to overcome resistance. One transmembrane transporter that contributes to chemotherapy resistance is P-gp, which releases medications from cells. (DOX + CUR)-FA-NPs increase drug accumulation in tumor cells and reduce resistance by blocking P-gp, which stops resistant cells from removing the medications [28]. Additionally, D-a-tocopherol polyethylene glycol 1000 succinate-resveratrol solid lipid NPs (TPGS-Res-SLNs) were developed by researchers, and they were successful in lowering the expression of proteins linked to multidrug resistance, such as GRP and BCRP. This decrease increases the concentration and duration of effect of chemotherapeutic medicines by reducing their excretion and inactivation within cells. Additionally, TPGS-Res-SLNs improved the effectiveness of chemotherapy by inhibiting the EMT in cancer cells, which decreased their capacity to invade and spread [29].

The main phases of hormone-independent BC carcinogenesis, which include angiogenesis, metastasis, cell proliferation, and survival, are all significantly influenced by cell signaling [30]. An overview of the role these signaling pathways play in chemotherapy resistance in BC is given in this section. It has been demonstrated that PI3K/AKT/mTOR signaling pathway dysregulation facilitates cancer spread and increases multidrug resistance. A pH-sensitive nanocomplex was created by Yin et al. to co-deliver siRNA and paclitaxel (PTX) to metastatic breast cancer. In 4T1 metastatic BC cells, the siRNA targets and inhibits Akt expression. Micelle/siAkt nanocomplexes (PMA) loaded with PTX effectively downregulated P-gp, boosted Caspase-3 production, and knocked down the Akt gene in these cells. In addition to showing encouraging in vitro outcomes, PMA proved to be safe and effective in vivo. PMA reduced lung metastases of BC by 96.8% and inhibited tumors by 94.1% in 4T1 tumor-bearing mice. Additionally, the PMA nanocomplex did not generate lesions in normal tissues and showed very low toxicity [31]. TNBC cells commonly overexpress Notch1 receptors and underexpress miR-34a microRNA, according to Guney et al. developed N1-34a-NPs by encapsulating miR-34a mimics in poly NPs in order to address this. In order to disrupt Notch signaling and the cascade that goes along with it, these NPs were functionalized to target the overexpressed Notch1 receptors on the surface of TNBC cells. Their results demonstrated that N1-34a-NPs efficiently controlled Notch signaling and its downstream targets in TNBC cells, leading to decreased migration and proliferation as well as cell senescence [32].

The present research has established the novel combined therapeutic approach involving both doxorubicin (DOX) and its dietary component, indole 3,3'-diindolylmethane (DIM). In this introduction of the two agents by loading them onto exosome-encapsulated mesoporous silica NPs (e-DDMSNP), DIM and DOX

were co-delivered to the cancer stem cell (CSC). This approach would increase specificity, stability, and homing potential towards the CSC niche for both DIM and DOX in vitro and in vivo. Thus, our innovative exosome nano-preparation holds good promise to target CSCs following the EMT process [33]. Targeting the EMT process using the inhibition by SKN, SKN@FPD NM is a nanodrug delivery method for metastasis risk reduction of BC cells. The combination further enhances tumor cell lethality while decreasing the probability of drug resistance and treatment failure [34]. In summary, nanodrug delivery devices hold promise for treatment resistance in BC. There are thus strong chances for these systems to be effective in conquering drug resistance in various types of cancer. Programmed DNA self-assembly of nanosystems loaded with Rab26 siRNA into NPs for drug resistance in lung cancer was developed by researchers [35]. In the same way, RAW-PANP can facilitate PTX and miRNA delivery, proposing a novel strategy to treat PTX-resistant TNBC. Beyond this, RAW-PANP can also serve as a competent platform for targeted therapy in TNBC [36].

Nanomaterials in breast cancer treatment

Nanomaterials can be categorized in several ways. A common classification divides them into zero-dimensional (0D) and one-dimensional (1D) types, as well as polymers, based on their structure. In addition, they can be classified according to their chemical composition into organic and inorganic groups [37]. Other classification criteria include the materials' origin, properties, applications, and morphology (**Table 1**) [38]. Chemically synthesized or naturally occurring compounds make up the majority of organic nanomaterials. They are a major target of nanomedicine research since they are biodegradable and often have lower cytotoxicity [39]. On the other hand, because of their exceptional biocompatibility, multifunctionality, and capacity to regulate drug release, inorganic nanomaterials are drawing interest for their potential in BC treatment [40].

Liposomes

The closed spherical vesicle structure of liposomes, which are nanocarriers made of a phospholipid bilayer, sets them apart. Liposomes can fuse with cell membranes because of their makeup, which is similar to biological membranes. This allows for the targeted release of medications into cells. They can improve drug loading, ensure sustained, controlled release of the drug, and encapsulate both hydrophilic and hydrophobic drugs [41]. In their discussion of liposomes' benefits for intracellular drug delivery, Boratto et al. emphasized how well they would work as carriers for BC treatment. They demonstrated improved cellular drug delivery, increased tumor accumulation, and a regulated release of DOX with their pH-sensitive liposome formulation (pHSL-TS-DOX). Additionally, pHSL-TS-DOX therapy caused cell cycle arrest, especially in the G1 phase, which could aid in reducing the growth of tumor cells [42]. Furthermore, Badr-Eldin et al.'s APA-functionalized liposomes (EGA-EML-APA) showed enhanced cytotoxicity against human BC cells. This was accomplished by

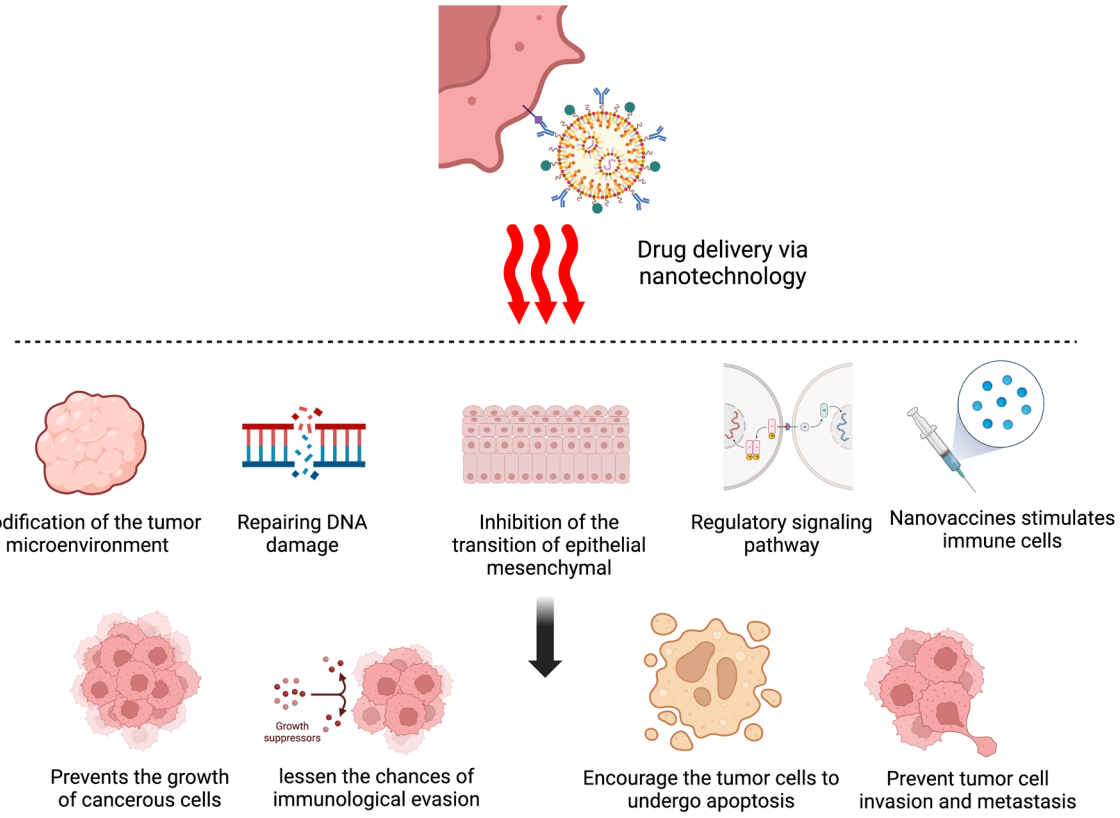

Figure 2. Novel nanodrug delivery techniques utilize a range of mechanisms to target breast cancer: immune system activation, apoptotic induction, tumor microenvironment manipulation, DNA damage repair, and metastasis suppression. Collectively, these mechanisms inhibit tumor growth, enhance treatment efficacy, and reduce the chances of drug resistance, laying the groundwork for advanced precision oncology options.

Table 1. Types of nanocarriers for drug delivery.

Nanomaterials	Structure	Features	Reference
Liposomes	Self-assembled closed colloidal structures are formed by lipid bilayer memberane	Bioabsorbable, extended period of circulation, bipolar	[81]
Polymeric micelles	Amphiphilic block copolymer is assembled to generate a hydrophilic shell and a hydrophobic core	Effective medication delivery method for hydrophilic substances, bioabsorbable, potential targeting, adaptive modification	[82]
Dendrimers	A synthetic polymer that forms a nanoscale branching structure with regular patterns and repeating units	Uniformity in branch length, size, and shape, altered biodistribution and pharmacokinetics, targeting, loading, and surface area are all increased	[83]
Carbon nanotubes	Carbon cylindrical structure formed by the benzoene ring	Water soluble, chemically modified, multifunctional, and bioabsorbable	N/A
Nanorods	Rod-shaped structures made of metals or semiconducting materials	Increased surface area, biocompatibility, targeted tumors, and efficient loading	[84]

causing MCF-7 cells to arrest in the G2/M and S phases, as well as by upregulating p53, bax, and casp3, downregulating bcl2, lowering NF-kB activity, increasing TNFa expression, and causing notable apoptotic events [43]. KLA-modified liposomes co-loaded with paclitaxel and 5-fluorouracil (KLA-5-FU/PTX Lps) were produced by Chen et al. and shown increased cytotoxicity against MDA-MB-231 cells. According to their suggested anti-tumor mechanism, the KLA peptide selectively targets mitochondria and facilitates liposome uptake by tumor cells. This causes the mitochondrial membrane to be disrupted, membrane potential to be lost, cytochrome C to be released, caspase-3 to be upregulated, and the apoptotic pathway to be activated in tumors. As a result, KLA-5-FU/PTX Lps offers a potentially effective treatment approach for TNBC [44]. When taken as a whole, these results highlight the substantial therapeutic potential of functionalized liposomes for breast cancer (**Figure 3**).

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are constructed of biocompatible physiological lipid components, making them extremely compatible with biological systems. To improve blood circulation and tumor selectivity, Granja et al. created SLNs that contain the anticancer medication mitoxantrone and functionalized them with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[folate (polyethylene glycol)] (DSPE-PEG-FA) ligands. By means of processes including clathrin-mediated endocytosis and macropinocytosis, this functionalization enhances cellular uptake while lowering systemic side effects [45]. In order to increase drug solubility and bioavailability and treat tumor cells more successfully, Aly et al. created CS/Lf/PTS-SLNs. By suppressing vascular endothelial growth factor, downregulating cyclin D1, and upregulating caspase-3 and BAX, these SLNs improve the effectiveness of medications [46]. Da Rocha et al.'s SLN-DTX promotes cell accumulation in the G2-M phase, boosts drug uptake in cells, and triggers apoptosis, all of which increase cytotoxicity. **Figure 1** illustrates the ways in which SLN-DTX suppresses tumor development, limits lung metastasis, decreases cell proliferation, enhances tumor cell death, and lowers BCL-2 expression [47]. According to Pindiprolu et al., PBA-Niclo-SLN reduces tumor recurrence in TNBC by inducing G0/G1 phase arrest and death, targeting STAT3, CD44/CD24 TNBC stem cell subsets, and altering markers of EMT [48]. According to these findings, solid lipid NPs have a lot of potential for use as therapeutic agents to treat BC and stop its spread and recurrence.

Dendrimers

Dendrimers NPs which usually range in size from 1 to 100 nm, are composed of three primary parts: a central core, repeating branching units, and outside surface functional groups [49]. Since the core of dendrimers is often hydrophobic, they are especially useful for increasing the solubility of hydrophobic medications [50]. Higher drug content and more effective targeted drug delivery are made possible by the diverse modification options provided by the branched architecture of dendrimers [51]. Additionally, medications, targeted ligands, and imaging agents can be coupled with or significantly alter the outer surface functional group [52]. Poly (L-lysine) (PLL) dendrimers, polypropylene imine (PPI) dendrimers, polyamidoamine (PAMAM) dendrimers, and PAMAM-organosilicon dendrimers (PAMAMOS) are often employed dendrimers in cancer treatment [49]. Due to so many of these odd characteristics the dendrimers are really apt for drug-delivery in cancer therapies. For instance, Guo et al. (2019) [53] developed a novel PAMAM dendrimer nanoparticle that had been modified with hyaluronic acid (HA) to deliver DOX and cisplatin in a combined manner (HA@PAMAM-Pt-Dox). The findings revealed that HA@PAMAM-Pt-Dox effectively wiped out BC cells and significantly enhanced the therapeutic effect of DOX and cisplatin.

Polymeric micelles

Polymer micelles are considered nanocarriers as they self-assemble hydrophilic shells with their hydrophobic cores [54]. Hydrophobic cores can be constructed from materials like PCL, PLA, or PLGA, whereas hydrophilic shells comprise materials like PEG, PGA, or even PEI [55]. Polymer micelles function with an average particle size of 5 to 100 nm, making them the best drug carriers penetrating tumor vasculature [56]. In addition, a hydrophobic core may hold various hydrophobic drugs in these micelles, which makes it very beneficial for the delivery of anticancer drugs like paclitaxel (PTX),

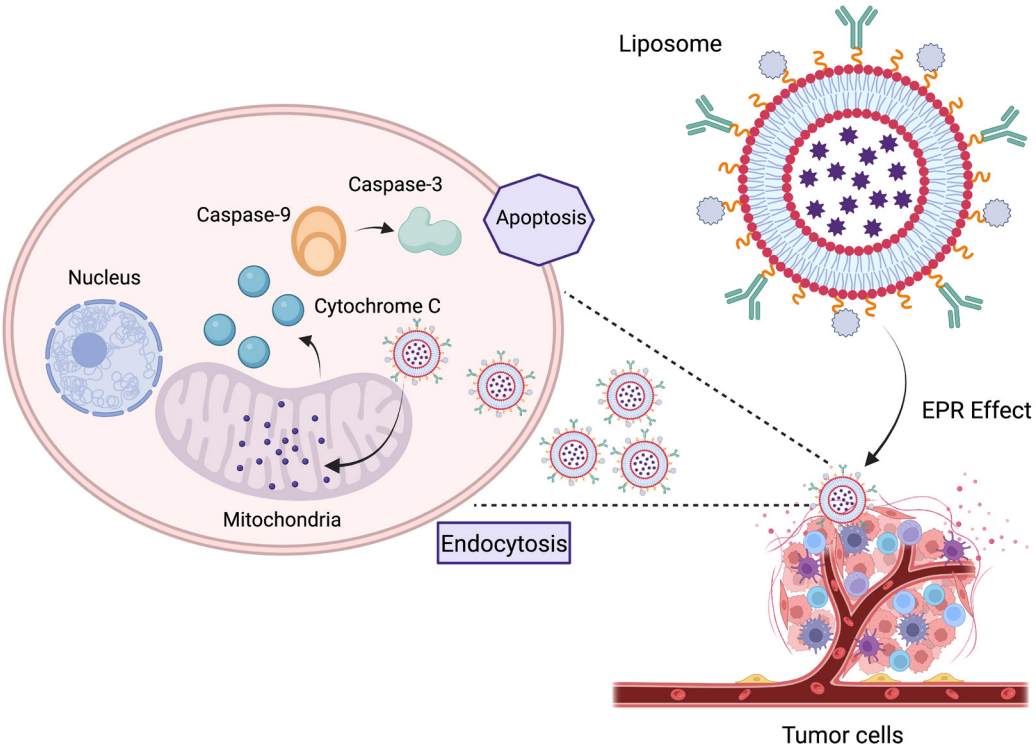

Figure 3. An improved liposomal nanocarrier technology designed for targeted mitochondrial distribution in breast cancer treatment is depicted in this figure. By using an EPR-driven uptake mechanism, the technology enables tumor cells to be selectively endocytosed. The nanocarriers deliver a multi-drug payload during intracellular trafficking, which causes ROS production, mitochondrial depolarization, and cytochrome C-mediated death. The strategy offers a promising path for next-generation cancer therapeutics by increasing therapeutic efficacy while reducing off-target damage.

which has low solubility in water. Peng et al. (2019) developed worm-like nanocrystal micelles from Herceptin-conjugated PTX-loaded PCL-PEG to treat HER2-positive breast cancer. Their results showed that the PTX-loaded micelles provided accurate targeting of HER2+ tumor cells while being safe for normal tissues and stable in both the tumor microenvironment and circulation [57].

Polymeric nanoparticles

Polymeric nanoparticles (P-NPs) can encapsulate or conjugate chemotherapeutic medications for distribution; they are made from biodegradable and biocompatible raw materials, usually polyesters (**Table 2**) [58]. However, regulating elements such the polymers' molecular weight, polydispersity, and stereoregularity is a significant issue in the production of P-NPs [59]. Nowadays, ring-opening polymerization of lactone or lactide monomers, assisted by organometallic catalysts, is a typical method for creating polyesters like polycaprolactone (PCL) and polylactide (PLA) [59]. Additionally, naturally existing biocompatible polymers with functional groups like ether, amide, and ester can be used to create P-NPs [59]. FDA-approved biocompatible polymers for drug delivery include PCL, PLA, and poly(lactic-co-glycolic acid) (PLGA); additional polymers used in drug delivery applications include polyethylene glycol (PEG), chitosan (CS), and hyaluronic acid (HA) [50]. Moreover, P-NPs can be designed to target particular areas and regulate drug release by changing the surface of these polymers or their characteristics with particular ligands, improving bioavailability and therapeutic efficacy [60].

Nanoparticles potential as a treatment for breast cancer

In addition to their diagnostic uses, NPs have the potential to revolutionize the treatment of breast cancer. They provide clear benefits in terms of drug delivery and chemoresistance, allowing for more specialized treatments that are more effective and have lower systemic toxicity [61]. In addition to the aforementioned trials, more than 60 albumin-based formulations are presently undergoing clinical testing with the goal of expanding on Abraxane's effectiveness.

One important illustration of the successful application of NPs in cancer treatment is Abraxane, an albumin-bound form of paclitaxel [62]. Through the increased permeability and retention (EPR) effect, this formulation passively targets tumor tissues by utilizing albumin's inherent characteristics. Because tumor areas frequently have impaired lymphatic drainage and vascular, the EPR effect is crucial for the buildup of therapeutic drugs in the tumor microenvironment. By enabling a greater concentration of the medication at the tumor site, passive targeting enhances treatment efficacy while reducing the harmful side effects frequently associated with systemic drug delivery [62]. Active targeting techniques are leveraged by newer nanoparticle formulations like ELU001 and CALAA-01, which are aimed to enhance the specificity of drug delivery by targeting molecules that are overexpressed on cancer cells [63, 64].

Passive targeting

The enhanced permeability and retention (EPR) effect is common

Table 2. Recent polymeric nanoparticles explored for breast cancer therapeutics.

Polymer	Drug	Preparation technique	Outcomes	Ref.
Polycaprolactone, PEG, stearic acid	Anastrozole	Solvent evaporation in direct emulsification	Increased effectiveness of treatment	[85]
PLGA, Labrafil M2125 CS oil	Baicalin	Nano-precipitation	Effective in enhancing anticancer potential	[86]
Bovine serum albumin	Curcumin	Desolvation	Treatment of breast cancer	[87]
PLA	Calcitriol	Nano-precipitation	Prolonged and sustained anticancer action; increased effectiveness of treatment	[88]
Bovine serum albumin, polyethylene glycol	Curcumin	Desolvation	Improved efficacy for breast cancer	[89]
Triethylamine, PLGA	Docetaxel	Solvent evaporation	Demonstrated a prolonged release, high affinity, and extreme sensitivity for cancer cells	[90]
Monophosphoryl lipid A	Doxorubicin	Conjugation (ROS switchable nano-platform)	Reduced systemic toxicity and effective tumor targeting	[91]
PLGA	Rapamycin	Single emulsion solvent evaporation	Drug targeted to epidermal growth factor receptor; efficient tumor selectivity	[92]
Pluronic F127	Paclitaxel, lapatinib	Thin-film hydration	Improved treatment for metastatic breast cancer	[93]
PLGA	Simvastatin	Spray drying with nanotechnology	Treatment of solid tumor	[94]
Alginate	Paclitaxel	Nano-emulsification polymer cross-linking	Improved breast cancer anticancer effects	[95]

passive targeting in cancer therapy. EPR works to increase delivery efficacy through unique tumor pathophysiological characteristics. The phenomenon can be seen in tumor tissues, where the newly formed blood vessels are even more permeable due to large fenestrations between endothelial cells when compared to that in normal tissues; this allows greater accumulation of the NPs in the tumor microenvironment [65]. The EPR effect is especially enhanced for about 10 to 100 nm-sized NPs because they won't be rapidly cleared by kidneys and will therefore be able to deposit greater payloads of the therapeutic agents into the tumor with lesser systemic toxicity [65].

The first FDA-approved medication based on NPs, Doxil®, contains liposomal DOX, which is intended to use the EPR effect to deliver medication specifically to BC patients. According to clinical research, Doxil® preserves its anticancer effectiveness while improving patient outcomes by lowering the cardiotoxicity linked to free DOX [66]. By altering the surface of NPs with hydrophilic polymers such as PEG, for example, it has been discovered that this reduces protein adsorption, which prolongs circulation time and increases tumor accumulation through the EPR effect. This strategy was successfully used in the formulation of Abraxane®, which exhibits improved tumor targeting and has been approved for the treatment of metastatic BC [62]. More sophisticated nanoparticle systems have been developed recently that further enhance the EPR effect.

More recently, it has been established that the EPR effect is impacted by the behavior of NPs in the tumor microenvironment, which is influenced by tumor pH, hypoxia, and enzyme activity. According to Chen et al., the tumor's acidic and hypoxic circumstances can be used to create pH-sensitive NPs that, when the pH drops, release their therapeutic payload, improving drug release precisely at the tumor site and hence improving therapeutic results [67]. Furthermore, current studies are aimed at improving nanoparticle design to overcome the difficulties posed by the EPR effect, including variations in vascular permeability and shifting interstitial pressures that may prevent nanoparticle penetration in specific malignancies. Strategies like as shape engineering, size modulation, and surface charge optimization are being researched to improve the therapeutic efficacy of passively targeted NPs in order to overcome these obstacles [65].

Passive targeting in conjunction with other therapeutic approaches has also attracted a lot of interest. It has demonstrated potential in increasing nanoparticle accumulation in tumors, for example, by combining it with hyperthermia, a condition in which localized heat momentarily improves vascular permeability at the tumor location. This enhances the therapeutic benefit without aggravating systemic negative effects. The study conducted by Basu et al. demonstrated that this synergistic mechanism indeed enhanced drug delivery to breast malignant tumors by combining magnetic NPs with localized hyperthermia [68]. The advances in the technologies that allow real-time monitoring of the efficiency of tumor targeting and nanoparticle distribution are further enhancing the possibility of passive targeting. The development of NPs with imaging capabilities that are trackable using imaging approaches such as magnetic resonance imaging (MRI), PET, or fluorescence imaging can serve as an illustration of this

advancement. This double work permits the tuning of individual therapy regimens, complementing the validation of nanoparticle accumulation at tumor sites. An effective mode of patient-tailored cancer therapy is provided by theranostics, a fascinating area of study that integrates therapeutic and diagnostics. For example, Chauhan et al. illustrated in a study of magnetic NPs in MRI and hyperthermia how the NPs could enhance drug delivery via the EPR effect while providing real-time assessment of therapeutic efficacy [69]. The combination of genetic engineering and nanotechnology is another interesting area of study for the treatment of cancer. For example, gene therapy can be used to target particular cancer cells, while sparing normal healthy tissues, by coupling it with such nanoparticle delivery technologies. Li et al. were able to deliver CRISPR-Cas9 systems targeting different oncogenes within BC cells with lipid-based NPs. Their results indicate that this may offer extremely effective and much less invasive alternatives to traditional radiotherapy and chemotherapy, thereby establishing a new gold standard in cancer treatment [70]. Combination therapy in which NPs are used to co-deliver several compounds at the same time has also shown much promise. Studies have shown that administering immunochemotherapeutics through NPs also greatly improved the therapeutic effect [71]. Maximization of distribution is then by enhancing the stability and circulation time of NPs. Encouraging results have come up with the latest innovations in coating material for NPs. New zwitterionic nanoparticle coating significantly reduced uptake by the mononuclear phagocyte system in an investigation by McMullen designed to prolong systemic circulation. This may enhance therapeutic index for anticancer drugs through higher concentrations of drugs at the tumor site [72].

Active targeting

Active targeting of drug delivery systems based on NPs for cancer therapy, requires molecules that can selectively identify and bind to receptors or biomarkers that are overexpressed on the surface of cancer cells. The objective of this approach is to improve the accuracy and potency of delivering the medicine to malignant sites. For instance, peptide or antibody-modified NPs that bind to transmembrane receptors associated with cancer are a means of targeting mainly cancer cells. This reduces side effects while at the same time enhancing the efficacy of anticancer treatments. Moreover, drug release from NPs can be regulated and sustained, hence eliminating the need for a regular dosing regimen. Furthermore, more sophisticated nanomedicine might be enabled to cross biological barriers, such as the blood-brain barrier, thus allowing targeted drug delivery with enhanced therapeutic effects [73].

Antibody fragments such as Fab, Fab', Fv, single-chain variable fragments (ScFv), and single-domain antibodies (or nanobodies) have been revealed recently to offer a novel dimension of opportunity as efficient targeting ligands on NPs [74]. The fragments derive benefits from easy genetic manipulation, economical manufacture, and highly specific targeting. Their reduced size gives them a distinct therapeutic advantage to make them user-friendly in multifunctional drug formulations and improves tissue penetration [75]. In addition, the results regarding the improvement of the specificity and efficacy of drug delivery through incorporating antibody fragments into whole nanoparticle systems have also been favorable. These conjugates have exposed much greater cytotoxicity and targeted efficacy against pancreatic cancer cells; therefore, they might also be relevant in treating BC [74].

This progress is demonstrated in a ground-breaking study by Marshall et al., which developed biomimetic, targeted theragnostic NPs for the treatment of breast cancer. The work used NPs modified with targeting ligands and coated with human red blood cell membranes, using biomimetic principles. These NPs showed a better capacity to target MCF-7 BC cells that express epithelial cell adhesion molecule (EpCAM) by encapsulating both chemotherapeutic drugs and imaging markers [76]. These NPs' dual purpose enabled accurate cancer cell imaging and targeted drug delivery, leveraging the special powers of nanoscale engineering to get beyond the drawbacks of conventional therapies. This strategy is a step toward personalized medicine, where tracking the growth of cancer can inform changes to treatment regimens for the best results. It also demonstrates the idea of theranostics, which is a blend of therapy and diagnostics [77]. This illustration shows how nanotechnology can support an all-encompassing approach to cancer detection and therapy.

One-of-a-kind unique excellence has been given to the field by Marshall et al. in their ground-breaking research involving the engineering of biomimetic and targeted theragnostic NPs dedicated to the treatment of breast cancer. These were developed according to biomimetic principles through the utilization of targeting ligand-modified NPs coated with human red blood cell membranes. These NPs targeted MCF-7 BC cells more efficiently as they were better than those not containing the encapsulated chemotherapeutics and imaging markers. Therefore, these NPs have made it easy to image the cancer cells and deliver the drugs targetedly, in nanoscale engineering that avoids some of the disadvantages of traditional therapies. This forms part of advances leading to personalized medicine where tracing the growth of cancer could determine timely changes in treatment regimens for the best possible outcomes. This is primarily the second aspect of what theranostics is all about; the amalgamation of therapy and diagnostics in one. This is an example of how nanotechnology could offer a synergistic contribution to cancer diagnostics and treatment efforts [78].

The creation of NPs that selectively target tumor-associated receptors is one recent advancement in this field. The application of ligands, such as antibodies, aptamers, or tiny molecules that attach to cancer-specific receptors, was a significant development in this area. For instance, customized NPs have been effectively used to target the HER2 receptor, which is overexpressed in around 30% of instances of BC [79]. Furthermore, new avenues for all-encompassing cancer treatment are being opened by the investigation of multifunctional NPs that combine targeted drug delivery with other therapeutic modalities, such as radiation or heat. Herea et al.'s noteworthy invention included magnetic NPs that were guided to the tumor site by means of external magnets. These NPs caused localized hyperthermia when exposed to alternating magnetic fields, which disrupted tumor cells and improved chemotherapeutic medication absorption, greatly increasing treatment outcomes [80].

Conclusions

Nanomaterial-based drug delivery systems hold significant potential for targeted cancer therapies, particularly in the treatment of breast cancer. As this technology continues to develop, its future application in cancer treatment looks promising. To enhance the system’s efficiency and broaden its clinical use, it is crucial to improve the retention of the drug and its stability within the circulatory system. Further research into the conjugation systems used to attach the drug to nanomaterials is needed to refine these systems for clinical trials and ensure greater precision in targeting. One potential solution to these challenges is combining nanomaterials with polymers like PEG, which aids in stabilizing the drug in circulatory fluids, ensures controlled drug release over time, and enhances targeting of cancer tissues. This polymer combination also improves the drug's half-life and viscosity, along

with that of lipid-based nanomaterials. These advancements are expected to improve the drug's efficacy and bioactivity. Eventually, comprehensive theranostic approaches to treating BC will be made possible by nanomaterial-based drug delivery systems that provide improved safety, effective targeting, and a strong drug-loading capacity.

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Ethics approval

No applicable.

Data availability

The data will be available upon request.

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Authors' contribution

Reem Al Yahyai contributed to draft, critical revision of the article, table making, and final submission; Jamilah Al Kalbani revised the manuscript and drew figures.

Competing interests

The authors declare no competing interests.

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