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Review Article

Comprehensive comparison of theranostic nanoparticles in breast cancer

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Abstract: Breast cancer is the most frequently happening cancer and the most typical cancer death among females. Despite the crucial progress in breast cancer therapy by using Chemotherapeutic agents, most anti-tumor drugs are insufficient to destroy exactly the breast cancer cells. The noble method of drug delivery using nanoparticles presents a great promise in treating breast cancer most sufficiently and with the least harm to the patient. Nanoparticles, with their spectacular characteristics, help overcome problems of this kind. Unique features of nanoparticles such as biocompatibility, bioavailability, biodegradability, sustained release, and, most importantly, site-specific targeting enables the Chemotherapeutic agents loaded in nanocarriers to differentiate between healthy tissue and cancer cells, leading to low toxicity and fewer side effects. This review focuses on evaluating and comprehending nanoparticles utilized in breast cancer treatment, including the most recent data related to the drugs they can carry. Also, this review covers all information related to each nanocarrier, such as their significant characteristics, subtypes, advantages, disadvantages, and chemical modification methods with recently published studies. This article discusses over 21 nanoparticles used in breast cancer treatment with possible chemical ligands such as monoclonal antibodies and chemotherapeutic agents binding to these carriers. These different nanoparticles and the unique features of each nanocarrier give the researchers all the data and insight to develop and use the brand-new drug delivery system.

Keywords: Breast cancer, nanoparticles, chemotherapeutic agents, immunotherapy, site-specific tumor targeting, targeted therapy

Introduction

Cancer immunotherapy is the non-natural stimulus of the immune system to cure cancer, boosting the immune system's natural ability to eradicate ailments, which is common in the treatment of bladder cancer, breast cancer, kidney cancer, cervical cancer, brain cancer, head and neck cancer and colorectal and esophageal cancers and many other types of cancer [1, 2]. Cancer immunotherapy has altered the standard for cancer cure; such treatments focus on enhancing anti-tumor immune reflexes with more insignificant off-target impacts than chemotherapies and some other mediators that straightly eliminate cancer cells [3-5]. This method has shown promising results in cancer remedies. Nevertheless, patient response rates continue to vary for reasons that are not well understood; however, there have been some assumptions for this phenomenon, such as immune competency and variety, differing antigen specificity and expression levels, and gut microbiota [6]. The use of cancer immunotherapy to trigger the immune system to identify and eradicate malignancies has provided novel promises for successful cancer treatment [7, 8]. Immunotherapies that increase the capability of endogenous T cells to terminate cancer cells have established therapeutic effectiveness in a diversity of human malignancies [9, 10]. Nanoparticles have lured significant consideration and display excessive potential in the field of malignancy immunotherapy. NPs used as transporters can carry immune cargo, such as antigens, gene therapeutics, and proteins to the intended position. Compared to specific immunotherapy, NP-based immunotherapy boosts a more brutal immune response and has higher specificity and effectiveness [11, 12]. Such nanosized structures are anticipated to partici-

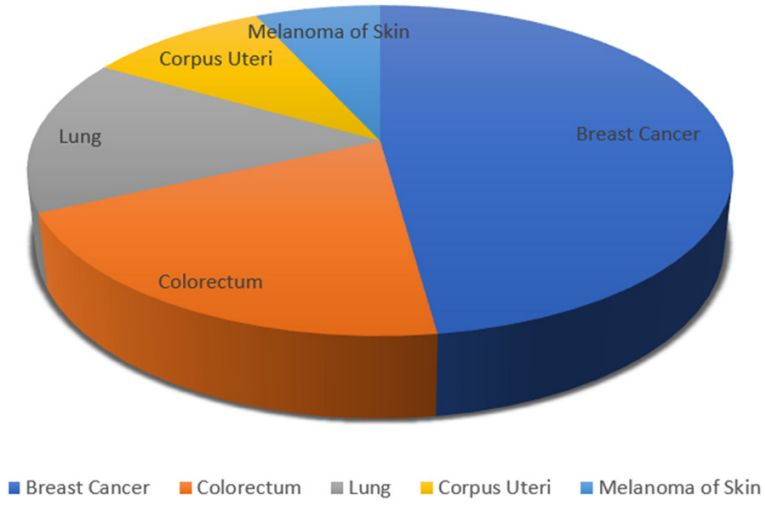

Figure 1. Most common cancers among women.

pate in imaging, pursuing, and observing abilities with the targeted transfer of mixtures to tumors, cellular purposes and procedures, or precise organs [13-17]. Breast cancer is a severe ailment in women and is the top reason for mortality. This malignancy is a heterogeneous illness, so stratification of tumors is essential to attain better clinical outcomes [18]. Metastasis is primarily responsible for its incurableness [19, 20]. Epidemiologic studies have acknowledged the diversity of breast cancer risk factors such as race, ethnicity, family history of cancer, genetic traits, and changeable contacts such as augmented alcohol consumption, physical sedentariness, exogenous hormones, and confident females generative factors [21]. Cancer immunotherapy is an innovative method that promotes the host immune system to identify and eliminate highly selected cancer cells. However, there is no comprehensive assessment of methods used to eradicate tumoral cells. This article tends to deliberate using of nanoparticles as too invasive tumoral cells and the effectiveness of this method. In this review, contemporary findings of nanomaterials used in breast cancer immunotherapy have been widely classified and extensively included through distinct sectors. These classifications are immensely helpful for a comprehensive understanding of used particles and mechanisms of theranostics in this era.

Breast cancer

Breast cancer is the most frequently happening cancer and is the most typical cancer death amole females. His disease is a multifaceted ailment that shows a considerable degree of inter- and intra-tumoral heterogeneousness [18, 22-25]. According to the data from WHO, in 2020, there were 2.3 million women identified with breast cancer and 685,000 losses worldwide. As of the end of 2020, 7.8 million females were thriving who were detected with breast cancer in the past five years, making it the world's most predominant cancer [26] (**Figure 1**). Breast cancer positions the fifth reason for mortality from malignancy. While it is the most common reason for cancer death in females in less industrialized districts, it is now the second cause of cancer death in more industrialized communities after lung cancer [27, 28]. There are numerous risk factors for breast cancer such as aging, genetic mutations, having dense breasts, the unique history of breast cancer or specific non-cancerous breast diseases, family history of breast or ovarian cancer, preceding treatment using radiation therapy, and consumption of diethylstilbestrol drug [29]. Breast cancer's common symptoms in women are a new lump in the breast or underarm (armpit), thickening or swelling of the breast, irritation of breast skin, redness or flaky skin in the nipple part of the breast, pulling in of the nipple or discomfort in the nipple area, nipple discharge except for breast milk, including blood, any alteration in the size or the shape of the breast, ache in any part of the breast [30]. The experiment of Joan R. Bloom showed that breast cancer exerts physical distresses and emotional distresses. Emotional support is particularly significant during the acute recovery period for one's mental health, whereas instrumental support gives promising results for women who have poorer physical and psychological healthiness [31].

Types of breast cancer

There are different kinds of breast cancer encompassing non-invasive and invasive cancers. Non-invasive breast cancer includes Ductal carcinoma in situ, and Lobular carcinoma in situ and invasive breast cancer contains

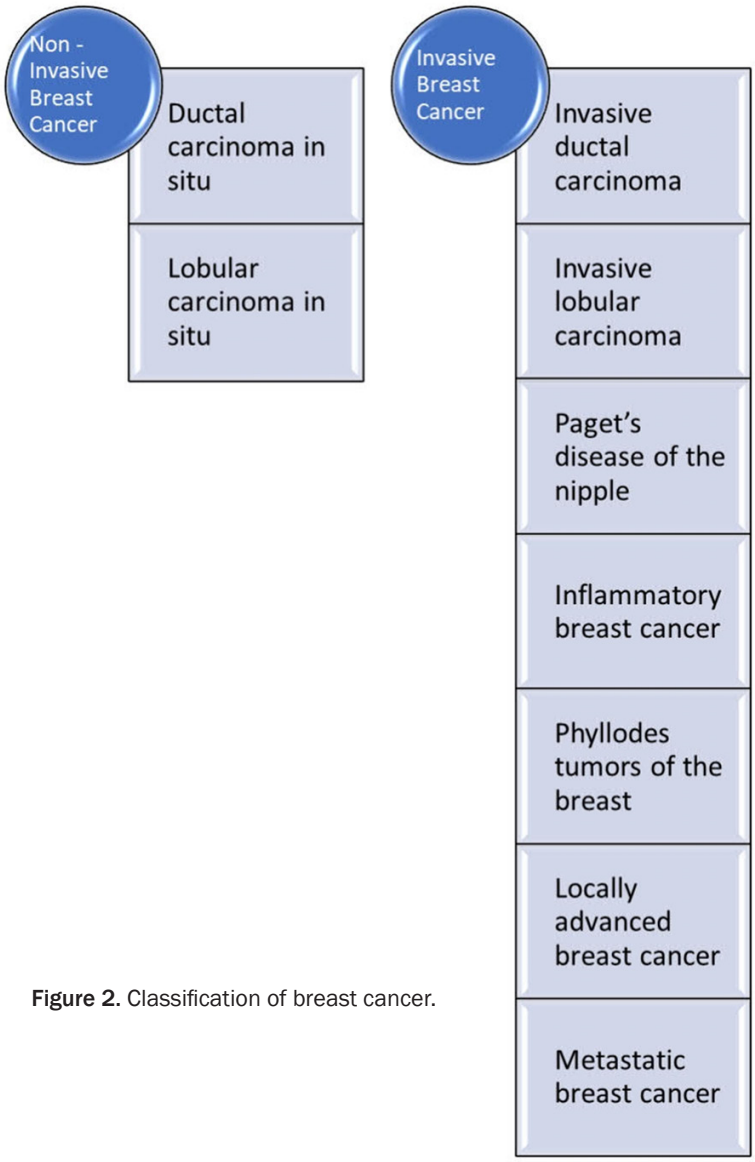

Figure 2. Classification of breast cancer.

Invasive ductal carcinoma, invasive lobular carcinoma, Paget's disease of the nipple, Inflammatory breast cancer, Phyllodes tumors of the breast, locally advanced breast cancer, and metastatic breast cancer [32, 33] (**Figure 2**).

In the past years, traditional classifications encompassing histological valuation and staging were applied to establish the patient's treatment method. Recently, molecular analysis of breast tumors has opened a gate for further understanding breast cancer biology and classification [34, 35]. Also, targeted-gene sequencing has emerged as the most novel and exact approach to determine the class of breast cancer. This next-generation method has helped extensively evaluate the mutations in breast tumor cells [36].

Molecular classification

Through molecular analysis of breast cancers with gene expression profiling, breast cancer could be sub-classified into diverse subtypes. Generally, these subtypes comprise luminal ER (estrogen receptor) positive (luminal A and luminal B), human epidermal growth factor receptor 2 (HER2) enriched, and basal-like or triple-negative [22, 37, 38]. Luminal A breast cancer is hormone-receptor-positive (estrogen-receptor and progesterone-receptor positive), HER2 negative, and has trivial levels of the protein Ki-67, which helps control how fast cancer cells grow [39]. Luminal B breast cancers are categorized by a minor ER expression, a slight progesterone receptor (PgR), and a high histologic grade [40, 41]. HER2-enriched breast cancer is hormone-receptor negative (estrogen-receptor and progesterone-receptor negative) and HER2 positive [42]. Triple-negative/basal-like breast cancer is HER2 negative and hormone-receptor negative (estrogen-receptor and progesterone-receptor negative) [43] (**Table 1**).

Targeted-gene sequencing

Targeted-gene sequencing is a revolutionary DNA sequencing practice aiming at amplicons and particular genes [44]. Comparing and analyzing the Genome of the DNA and gene expression of primary cancer cells and metastases in numerous cases can help estimate the mechanisms that cause metastasis [45]. In addition, targeted-gene sequencing has facilitated the prediction of future recurrence sites [46, 47], precise treatment based on molecular features, response to therapy, and survival [48].

Table 1. Classification of molecular subtypes

Molecular subtype	ER-estrogen receptor	human epidermal growth factor receptor 2	PR-progesterone receptor	Ref.
Luminal A	positive	negative	positive	[39]
Luminal B	minimum	positive/negative	minimum	[40, 41]
HER2	negative	positive	negative	[42]
Triple-negative or basal-like	negative	negative	negative	[43]

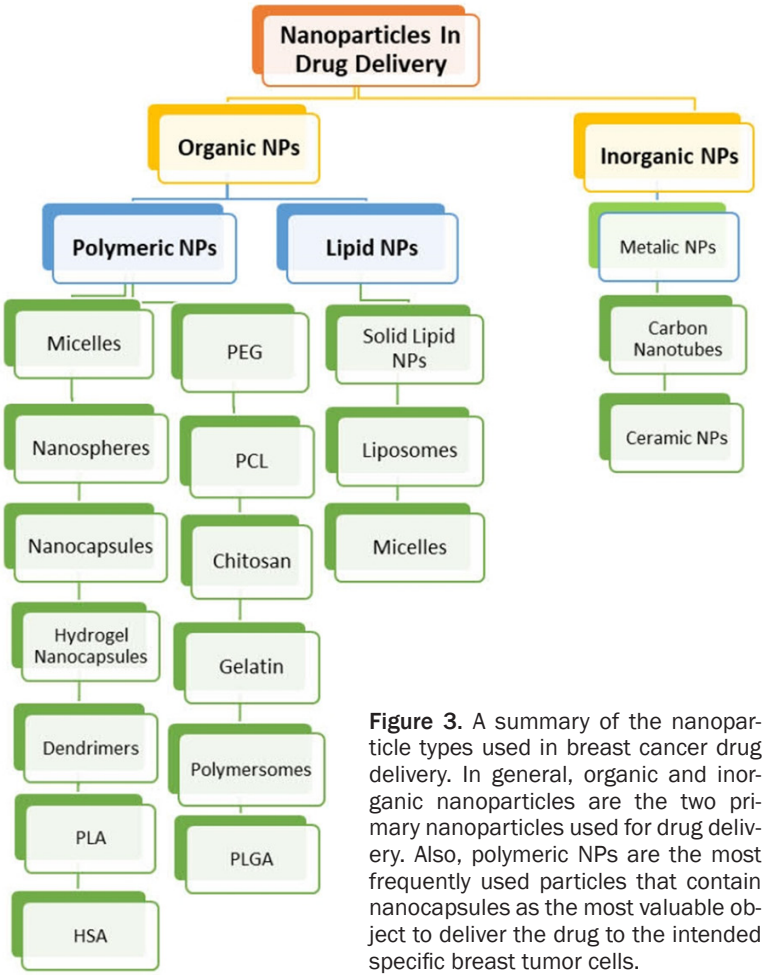

Figure 3. A summary of the nanoparticle types used in breast cancer drug delivery. In general, organic and inorganic nanoparticles are the two primary nanoparticles used for drug delivery. Also, polymeric NPs are the most frequently used particles that contain nanocapsules as the most valuable object to deliver the drug to the intended specific breast tumor cells.

Targeted gene sequencing panels are used to determine the exact mutation in a sample. Focused conferences hold the genes or regions suspected to cause breast cancer [49].

Classification of particles

Microparticles used in drug delivery

Microparticles (MPs) are dense or dispersed particles ranging from 1 to 1000 μm [50]. The medication is dissolved, trapped, encapsulated, or connected to a microparticle matrix. Dependent on the technique of composing, microparticles, microspheres, or microcapsules can be produced [51, 52]. Like nanoparticles, microparticles are used as drug transporters or as adjuvants for vaccines. The medications or antigens may combine into particles in the shape of a dense dispersion or a solid solution [53]. Also, they may be adjoined to the particle exterior by physical adsorption and chemical attaching [54]. These transportation systems present several benefits contrasted to common dosage forms, which contain enhanced effectiveness, decreased toxicity, and bettered patient convenience [55]. Some critical challenges confronting immunotherapy include inaccurate toxicity and inexact immune activation [56]. To help undertake this problem, nanoparticles and microparticles play an essential role as effective drug transporting structures for immunotherapies to regulate the immune system [57]. N.P./MPs include many kinds; the most important ones are polymeric particles and liposomes. The majority of the typical polymeric particles are composed of chitosan, biodegradable polyesters, altered Dextrans, and Polyketals [58]. Most of the biodegradable polyesters (e.g., poly lactic-co-glycolic acid (PLGA)) are drug delivery tools that are approved by Food and Drug Administration [59].

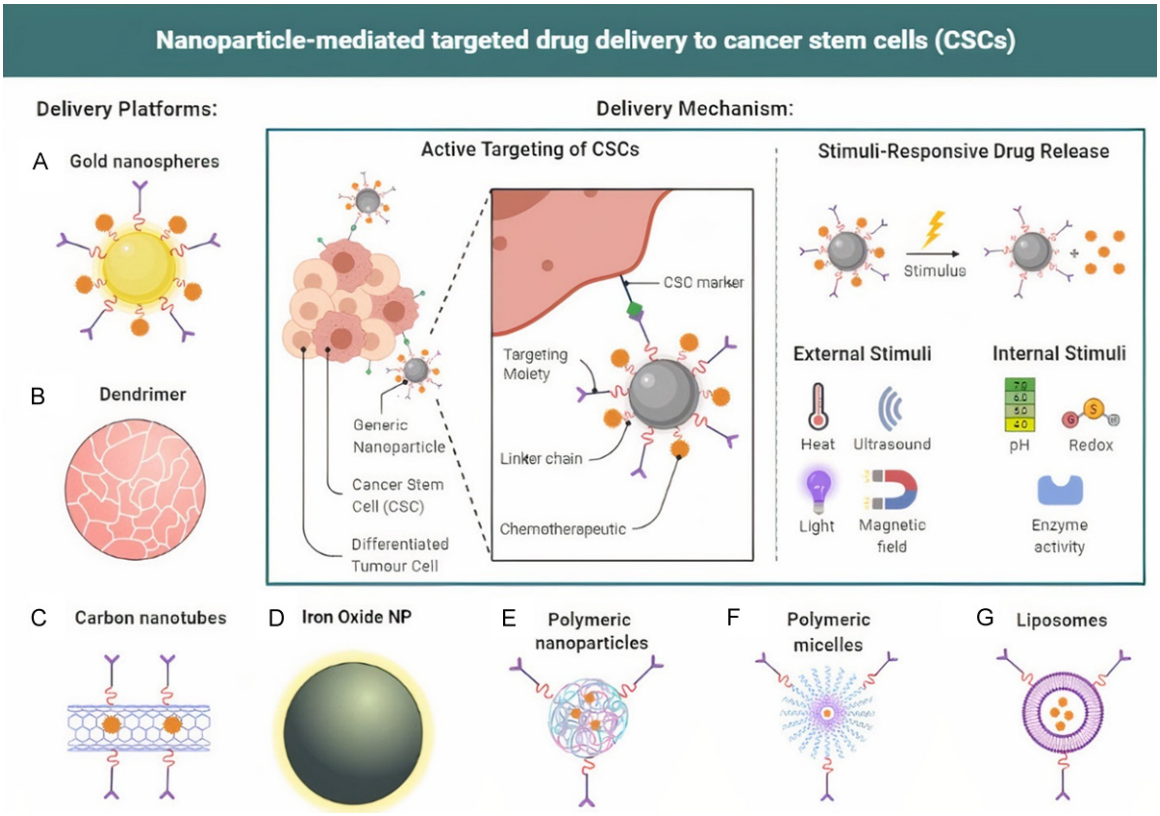

Figure 4. It indicates nanoparticle-mediated drug delivery to tumor cells, especially breast cells and summarizes how NPs reach the target organ and stimulate the destination cells. NPs have been utilized for effective drug delivery, analytic tools and facilitate an efficient, targeted biomolecular interface to lessen side effects caused during the treatment.

Nanoparticles used in drug delivery

Nanoparticle drug delivery systems are professional methods that transport medication to the intended cells and control the release of drugs [60]. The recent procedure of a drug delivery method tends to lessen side effects and decrease the dosage. Lately, different NPs, as depicted in (**Figure 3**), have stimulated interest because of their possible use for efficient drug delivery [61]. Boosting ligand binding effectiveness can reduce dosage and decrease NP. Toxicity Reducing dosage or dosage frequency also lessens the mass of nanoparticles per mass of medication; therefore, attaining more energy [62]. According to the characterization from NNI (National Nanotechnology Initiative), nanoparticles are systems of sizes fluctuating between 1 to 100 nm in as a single minimum dimension [63].

Nevertheless, the prefix "nano" usually refers to particles up to several hundred nanometers in size. Nanoparticles with enhanced physicochemical and biological features are absorbed in cells more effortlessly than giant molecules [64]. Thus, nanoparticles could be effectively utilized as transporting means for presently accessible bioactive compounds [60]. NPs can load different components at the same time for simultaneous transport, keep the loads from degradation and early release, and inactively or actively target cancer cells by the enhanced permeability and retention (EPR) influence or surface alteration by ligands correspondingly [61] (**Figure 4**). Also, inorganic nanoparticles could be utilized as a local source of ICD-inducing cure or focus attention on a treatment by external energy fields to diminish harm to normal cells [65, 66].

Due to the lack of full clinical application support and intratumorally administration of these nanoparticles, most nanocarriers' use remains only in vivo and in vitro stage. According to the academic journals, there has been a hope that

vascular interventional administration might be a possible solution to utilize NPs by locating the tumor-feeding vessels [67]. A summary in (**Table 2**). is brought to compare these nanoparticles in detail.

Organic nanoparticles

Organic nanoparticles are developed upon organic or synthetic organic molecules. Nature provides many examples of organic NPs like protein combinations, lipid bodies, milk emulsions, or more intricate prepared structures such as viruses [68, 69]. The principal value of devising medications into nanoparticles is enhancing particle exterior surface in touch with the dissolution agent, enhancing bioavailability. Numerous drugs have been formulated with this method and are available [70]. By using an innovative technique called SMILE (Stabilized Metal Ion Ligand complex), Scientists have produced a biomimetic nanoparticle formulation of Cu(DDC)2 to overcome drug delivery issues [71]. Cu(DDC)2 metal-organic compound core and surface covered bovine serum albumin (BSA) are integrated to make Metal-organic Nanoparticle (MON), which efficiently prevents the outgrowth of breast cancer cells [72, 73].

Polymeric nanoparticles: Polymeric NPs have drawn significant attention over the latest years because of their features due to their tiny scale [74-76]. Possible usage for controlled drug release, the capability to retain medication and other molecules with biological function from the environment, enhance their bioavailability, and therapeutic index are benefits of polymeric nanoparticles in drug delivery [77]. Nanocapsules and Nanospheres are two types of polymeric nanoparticles. Polymer nanoparticles are one of the most advanced non-invasive methods for drug delivery uses [78]. Polymeric nanoparticles are units within the size variation from 1 to 1000 nm and can be filled with effective compounds trapped inside or surface-adsorbed onto the polymeric core [77]. Polymeric nanoparticles can control drug release either by diffusion via polymer matrix or matrix degradation. They have been inspected as drug-delivery systems for the site-specific targeting of cancer cells [79]. The most significant benefits for these particles are supplying controlled release to the preferred site, supply stability to labile molecules (e.g., proteins), and supply capability to alter surfaces with ligands for stealth and targeted drug delivery goals [80]. Due to the poor water-solubility, three of the most critical drugs in breast cancer delivered by polycaprolactone-polyethylene glycol (PCL-PEG) nanoparticles are Cisplatin, Doxorubicin, and 5-fluorouracil. PCL-PEG is a polymeric nanoparticle that increases the stability and solubility of drug molecules to enhance drug delivery systems [81, 82]. Bressler and his colleagues have shown that AXT050 is a multimodal peptide with anti-tumorigenic and anti-angiogenic properties by targeting integrin αVβ3 on the surface of cells in culture. It also can target and disturb both cancer cells and endothelial cells; therefore, this technology may be capable of administrations in cancer nanomedicine [83]. Abou-El-Naga's experiment has represented that cellular uptake of Docetaxel was time-dependent and reached the maximum after conjugating on PLGA NPs and with folic acid combination, which triggered the endocytosis mechanism; therefore, folic acid/PLGA NPs can have a promising drug delivery system for Docetaxel in breast cancer treatment [84]. Soe ZC and her colleagues' study has shown that transferrin-conjugated polymeric nanoparticle-targeted NP used as a doxorubicin carrier into a drug-resistant cell line has (a transferrin (Tf)-conjugated polymeric nanoparticle composed of poloxamer 407 (F127) and 123 (P123) (Dox/F127&P123-Tf)) improved cellular uptake and tempted prohibition of cell propagation in vitro, not only in doxorubicin-sensitive cells but also in the doxorubicin-resistant in a particular type of breast cancer cells. Hence, transferrin-targeted NPs can be utilized as harmless and effective drug carriers to treat doxorubicin-sensitive and resistant breast tumor cells [85].

(1) PEG: The most helpful polymer for drug delivery is Polyethylene glycol (PEG) because of its unique behavior that prevents early recognition by the immune system (opsonization) [86]. Also, the hydrophilic characteristic of PEG leads to stabilizing nanoparticles by steric and not ionic effects, especially in water [87]. Carrying PEGylated nanoparticles with drugs to epidermal growth factor receptor (EGFR) + Triple-negative breast cancer (TNBC) requires binding PEG engager to polyethylene glycol and EGFR simultaneously. Enhancing the anti-proliferative activity of PEG-liposomal doxorubicin by PEG engagement in EGFR+TNBC cells brings

Table 2. The summary of the advantages and disadvantages of each nano-carriers with their variable size

Np Type	Size	Advantage	Disadvantage	Ref
Polymeric Nanoparticles		Biodegradable, biocompatible, Efficacious distribution of both water-soluble and insoluble medications.	Cytotoxicity, Organizational heterogeneity as reproduced by high polydispersity index.	[229]
Nanospheres	100-200 nm	Significant external to volume ratio, Measured release of insoluble actives.	Absence of Stability of some actives, High manufacture expenditure.	[230-232]
Nanocapsules	5-1000 nm	The usage of natural polymers such as polysaccharides and proteins can rise bioavailability and biodegradability.	Extensive dispersal of condensed actives, a purification procedure is required after the synthesis of nanocapsules.	[232-234]
Dendrimers	1-100 nm	Functionalization of outlying groups control solubilization and permits targeted delivery of load-Appropriate for combining lipophilic and lipophobic cargo.	Toxicity linked with surface amin groups-Pharmacokinetics, biodistribution, biodegradation, and chronic toxicity of PAMAM is not understood yet.	[235]
Micelles	20--100 nm	Self-assembling, thermodynamic constancy, targeting potent.	Selection of appropriate surfactants.	[236]
Polymersomes	100 nm to a few μm	highly adaptable and biologically steady systems and their overall possessions and drug encapsulation and release competencies can be effortlessly tuned by applying numerous block copolymers that are biodegradable and/or stimuli-responsive.	More clinical studies are vital for its formation as gold standard avenues.	[237]
Solid lipid Nanoparticles	50--100 nm	Progresses solubility in water of hydrophobic cargo, Hydrophilic cargo conceivable, Relatively low-cost manufacture, Biocompatible/biodegradable, Possible production scaling-up.	Recrystallization danger and little encapsulation load, High water content in dispersals (70-99.9%), Premature cargo release during storing.	[238, 239]
Liposomes	30 nm to a few μm	Effective delivery of both water-soluble and insoluble drugs, simply tailored size and carrying capacity, Significant construction.	Swift release, Petite shelf lives, Variability, clearance to reticuloendothelial structure.	[229, 240, 241]
Metal Nanoparticles	1 nm to a few hundreds of nm	Uniformity in scope, shape, and branch length Tuned p harmacokinetics and biodistribution Augmented surface area, enlarged loading Targeting is achieved.	Poisonous effects on the body.	[229, 235]
Carbon Nanotubes	About 0.7 nm	Multiple roles Chemical alteration Water soluble and biocompatible Efficient cargo.	Poisonousness.	[235]
Ceramic Nanoparticles	1--100 nm	Do not swell or change porosity and are steady at numerous pH and temperatures.	Sluggish biodegradation or non-degradation.	[242, 243]
Human serum albumin (HSA) Nanoparticles	66.5 kDa	Low toxicity, biodegradability, reproducibility, manageable release, and numerous drug binding sites.	the potential risk of pathogen contamination (e.g., HIV, hepatitis, CJD), side effects.	[219, 221]

Overall, the benefits overcome the drawbacks; however, the extended use of some nanoparticles is limited due to the toxicity.

about a reduction in breast tumor cells' growth and reductions in their number [88-90].

(2) PCL: Poly-ε-caprolactone (PCL) is another frequently used polymer nanocarrier decomposed by hydrolysis of its ester. Versatile nature, ease of fabrication, and biocompatibility are the features that have made PCL the center of attention in nanoparticle drug delivery [91, 92]. This nanocarrier is most suitable for long-term delivery up to one year because of its unique characteristic in slow biodegrading compared to other polymers [93]. NPs based on Poly (ε-caprolactone)-Poly (ethylene glycol)-Poly (ε-caprolactone) (PCL-PEG-PCL) can efficiently deliver Doxorubicin (DOX), an anthracycline anti-cancer drug, to the targeted breast tumor cells [94]. A study has shown synthesis of robust docetaxel/aptamer-polydopamine (DTX/Apt-pD)-CA-(PCL-*ran*-PLA) NPs with star-shaped CA-(PCL-*ran*-PLA) copolymers, which could be practical as optimistic targeting drug delivery systems for synergistic chemo-photothermal therapy of breast cancer [95].

(3) PEG-PCL: Cuong N-V and colleagues showed that three biodegradable PEG-PCL-PEG triblock copolymers with many PCL blocks were manufactured to transport anti-cancer drugs. The structures of copolymers were characterized by proton nuclear magnetic resonance, Fourier transforms infrared spectroscopy, gel permeation chromatography, differential scanning calorimetry, and X-ray diffraction, correspondingly. These hydrophobic PCL elements contained copolymers that could compress DOX into the micelle cores. The cytotoxicity of DOX-loaded micelles was higher than that of free DOX in specific breast cancer cells. These explanations show that DOX-loaded micelle is a hopeful means of treating multidrug-resistant tumors [96]. Additionally, in a study, mPEG-PCL copolymer was created. The copolymer mPEG-PCL was self-assembled into polymersomes in an aqueous solution in the presence of Methotrexate. Assays showed that methotrexate-loaded mPEG-PCL polymersomes had more prohibition effects on breast cancer cells than free Methotrexate, providing an appropriate and proper system for delivering Methotrexate to the breast cancer cells [97].

(4) Chitosan: Chitosan is a polymeric nanocarrier that is biodegradable, biocompatible, and vastly used in drug delivery with diverse administration methods. Positive surface charge and mucoadhesive feature enable chitosan NPs to connect to mucus membranes and release the loaded drug in a sustained release way [98, 99]. Other beneficial characteristics of chitosan are low immunogenicity and high biocompatibility, along with a high cationic charge [100, 101]. Additionally, chitosan is used to overcome the drug resistance and increased toxicity of some sufficient anti-cancer medications such as 5-Fluorouracil and doxorubicin [102]. A water-soluble product of chitosan called carboxymethyl chitosan (CMCS) can load 5-Fluorouracil and doxorubicin and facilitate the sustained release of these drugs [103]. Mono-dispersed and pH-sensitive chitosan silica hollow nanospheres ($CSeSiO_2$ HNPs) have shown promising results in breast cancer therapy. Antibody molecule (to ErbB 2) is conjugated with SiO_2 HNPs to a pH-sensitive polyelectrolyte layer to make a suitable nano-transporter for targeted TNF drug transport to breast cancer cells [104, 105]. In Santos-Carballal B's study, chitosan oligosaccharide (COS) showed promising results in preventing the aggressive capability of MDA-MB-231 breast tumor cells, which leads to a reduction in the metastasis process [106]. Even in Cancer gene therapy, chitosan is outstandingly valuable through specific nano complexes like chitosan-hsa-miRNA-145 (CS-miRNA), which downregulates the target mRNA proliferation in MCF-7 breast cancer cells [107].

(5) Gelatin: Gelatin is a versatile and natural biopolymer that has numerous significant functions because of its low price, easy accessibility, biodegradable and biocompatible characteristic, non-toxicity, easy adhesion, and adjusting chemically and consequently has a vast capacity to be utilized in drug delivery systems such as nanoparticles which contain protein [108-110]. Amifostine is used to firmly connect a targeting ligand (Herceptin) to amphiphilic gelatin (AG)-iron oxide calcium phosphate (CaP) NP which produces a nanoparticle system with a pH-sensitive CaP shell and degradable AG core, enabling the manageable sustained release of the two medicines [111]. A bioligand and magnetic targeting with the dual-targeting system of AGIO@CaP-CD (HER-AGIO@CaP-CD) led to a considerably high cellular uptake in HER2-overexpressing SKBr3 cells and more effective treatment for breast cancer [112].

(6) Poly-D, L-lactide-co-glycolide (PLGA): Because of the adjustable and sustained-release characteristics, low toxicity, and biocompatibility with tissue and cells, US Food and Drug Administration have approved Poly PLGA as one of the most efficient biodegradable polymeric NPs to be utilized in drug delivery structures [113]. Hydrolyzed PLGA in the body produces lactic acid and glycolic acid, biodegradable metabolite monomers. The body deals with these two monomers so quickly, leading to the low toxicity of PLGA [114]. Also, in cancer treatment, incorporating Docetaxel into the rod-shaped PLGA improves the efficacy of taxane-resistant triple-negative breast cancer [115].

(7) PLGA-PEG polymeric nanoparticles: In Akbari E's research, trapoxin/Methotrexate-co-loaded PLGA-PEG NPs were synthesized. The trapoxin/Methotrexate co-loaded PLGA-PEG displayed high growth inhibition against breast cancer cells; consequently, it showed good accomplishment, which supports using the system as a good candidate in the synergistic delivery of antineoplastic agents to treat breast cancer [116]. In another experiment done by Amirsaadat S and colleagues, PLGA-PEG NPs were used to co-deliver two natural anti-cancer agents, Metformin and Silibinin, against breast cancer cells. Outcomes disclosed that the encapsulation of Metformin and Silibinin in PLGA-PEG NPs could efficiently hinder the propagation of breast cancer cells than their pure forms [117]. Jusu SM and colleagues experimented with releasing targeted and untargeted (PGS and PTX) cancer drugs from physical blends of PLGA and PEG microparticles. The outcomes presented that the composite microcapsules allow the prolonged release of cancer drugs (PGS, PTX, PGS-LHRH, PTX-LHRH) over time that could significantly ease the localized treatment of TNBC [118]. Results show that nanochrysin or chrysin-loaded PLGA-PEG used in T47D and MCF7 cell lines apply a repressing effect on the two breast cancer cell lines, further than that of pure chrysin. Based on these outcomes, nanochrysin can be utilized for breast cancer therapy and proposes a novel and effective drug delivery system to contest breast cancer [119]. In Cao D's work, injectable liposomal doxorubicin-loaded PLGA-PEG-PLGA thermogel was synthesized. Liposomal doxorubicin-loaded thermogel exhibited protracted release of DOX deprived of separate initial burst compared with DOX-Gel. This study suggests that a hybrid medication delivery system containing liposome and hydrogel can sustain and enhance drug release, improving the anti-cancer effectiveness through localized therapy and reducing cytotoxicity [120]. Tabatabaei Mirakabad FS's study showed that curcumin-loaded PLGA-PEG nanoparticles have an inhibitory effect on the MCF-7 breast cancer cell line more than pure curcumin [121].

(8) Polylactic acid (PLA): PLA is a thermoplastic polyester nanoparticle that has drawn attention due to its biocompatibility, non-toxicity, and biodegradability features. Poly-lactic acid nanoparticles (PLA-NP) are commonly used as nanomedicines because of their benefits over metallic NP, such as keeping anti-cancer drug loads for sustained periods [122]. The anti-cancer drug paclitaxel (PTX) can be loaded to PLA/hydroxyapatite (HAp, which exhibits pH sensitivity) core-shell nanoparticles and facilitate effective drug delivery via the EPR effect to the breast tumor cells [123].

(9) Nanosphere: Nanospheres must be assumed to the matrix-based structures [124], which are different in size from 10 to 200 nm in diameter and can be crystalline or amorphous. They integrate with drugs, dissolve, encapsulate, or join bioactive to the polymeric matrix compound. These NPs guard bioactive and keep them from degrading chemicals and enzymes [125]. Hollow carbon nanospheres (HCNs) modified with anti-HER2 antibody and loaded with DOX facilitates the drug delivery (**Figure 5**) to the specific HER2-positive breast cancer cells and considerably restrain the tumor cells in vitro, causing ~a 60% decrease in the size of the HER2-positive tumors in vivo [126]. To overcome some of the typical restrictions of breast cancer treatment like off-targeted drug delivery, fast drug clearance, and drug resistance, porous magnetite nanospheres are used to load Doxo with great effectiveness for targeted drug transport to breast cancer cells depending on pH-sensitive drug release [127].

(10) Nanocapsule: A polymeric nanocapsule is a liquid or solid core with a polymeric shell covering the whole structure, its main difference from the nanosphere (**Figure 6**) [128]. These nanoparticles can transport enzyme biocatalysts, drugs, and vectors to tumor cells [129].

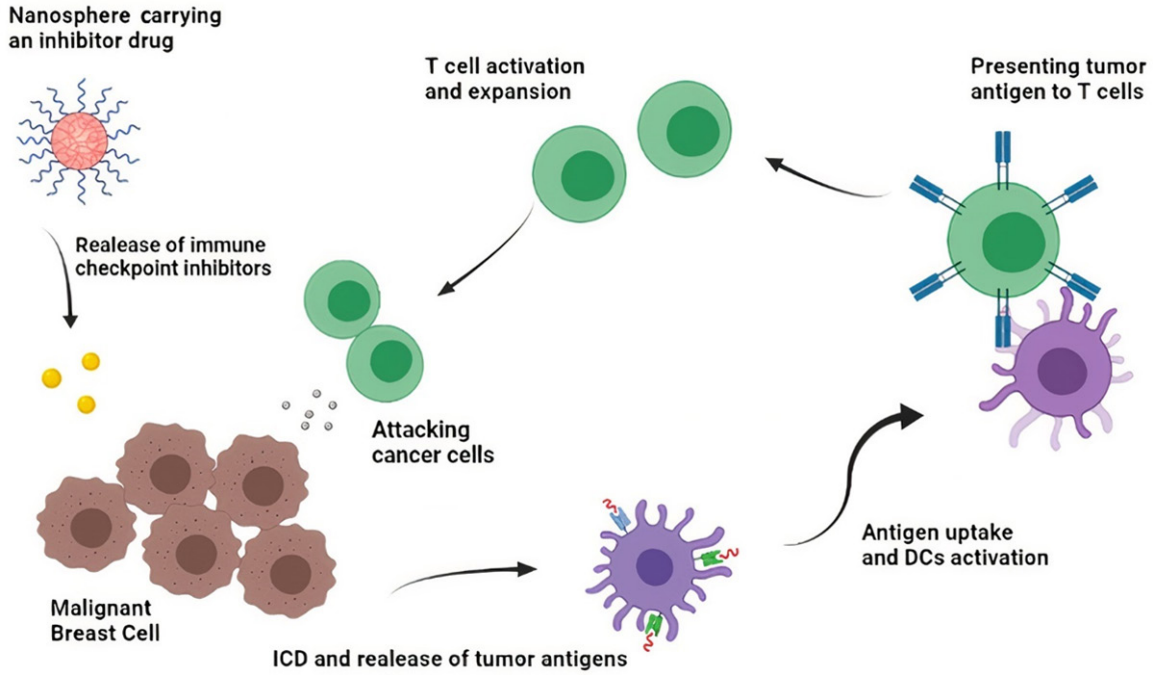

Figure 5. It summarizes the two agents working together to fight against breast tumor cells. The first one is the body's immune system which produces CD8+ T cells based on the antigen of the tumor cells presented by DCs to T cells. The second agent is immune checkpoint inhibitors delivered by nanoparticles to the organ. CD8+ T cells are then capable of attacking cancer cells and eliminating them with the help of immune checkpoint inhibitors carried to the position by nanoparticles like nanosphere.

They have a spherical form; drugs are located in the unfilled center and coated with polymeric shells [130]. The size of these particles differs from 50 to 300 nm. Nanocapsules can transport both hydrophilic and lipophilic drugs [131]. Lipid nanocapsules can efficiently transport hydrophobic drugs like Docetaxel and Thymoquinone to the intended breast tumor cells. These nanoparticles considerably improve the anti-tumor effect of free Docetaxel in breast cancer cells [132]. Utilizing Chitosan Grafted Lipid Nanocapsules loaded with Docetaxel and Thymoquinone is a novel method to enhance chemotherapeutic effectiveness in treating resistant breast tumor cells, which has shown promising results both in vivo and in vitro [133].

(11) Dendrimers: Dendrimers are created of repeating components, like polymers. However, they are significantly different from usual polymers by two key features: dendrimers are never produced by polymerization reactions, but they have a flawlessly devised and vastly reproducible structure and a very branched 3D design because of the usage of at least one kind of branching components as construction blocks for their synthesis [134, 135]. The main difference between these two is that a dendron usually has a sole chemically addressable assembly called the focal point or core. Dendrimers are built by adding layers to the branching groups [136]. The construction of dendrimers includes a core molecule with branching groups to which different branching molecules are attached in layers [137]. Because of their low toxicity, a polymeric dendrimer is of significant attention in biomedical uses such as polyamidoamine (PAMAM) dendrimers [138]. In HER2-positive breast cancer, Trastuzumab (TZ)-grafted dendrimers significantly enhance the transport of Docetaxel (DTX) to the tumor cells. These nanoparticles lead to higher antiproliferation activity, cellular internalization, and induction of apoptosis against HER2-positive breast cancer cells [139-141].

(12) Micelles: Polymeric micelles are widely investigated transporters to carry weakly water-soluble medications [142]. Amphiphilic block copolymers shape Polymeric micelles nano-sized core/shell systems. The reasons that

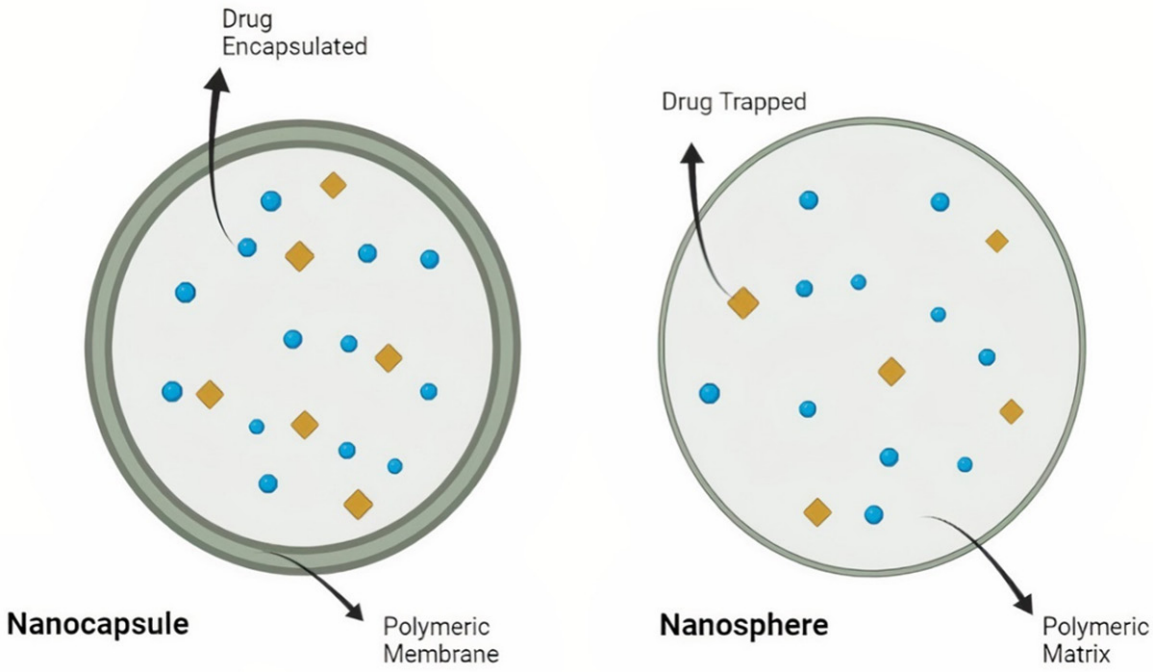

Figure 6. The main differences between nanosphere and nanocapsules. Nanocapsules have vesicular structures that a drug is loaded in the unfilled center and coated with a polymeric shell, while nanospheres matrix-based structures with a drug dispersed in it physically.

make these nanoparticles exceptionally well suitable for drug delivery uses are both the natural and adjustable features of polymeric micelles [143]. Polymeric micelles are applied in drug delivery because of their appealing qualities, like biocompatibility, less toxicity, core-shell assembly, micellar association, morphology, nano size, and relatively high steadiness [144]. The fundamental notion in this method is receptor-mediated endocytosis. The ligands coupled to the micelles attach to their exact receptors on the cell membrane, leading to the micelles' endocytosis [145]. The variation in mass between the micelles and universe enables them for extended circulation in the blood with escaping of renal clearance, yet permits for a means of eliminating the surfactant from the body when no longer needed [143]. IR780 iodide, a near-infrared (NIR) dye delivered to the tumor cells by micelles, has shown magnificent ability in the phototherapy of cancer cells. Herein, amphiphilic 28 micelles based on D-a-tocopheryl polyethylene glycol succinate (TPGS) and D-a-tocopheryl succinate 29 (TOS) can carry IR780 to the targeted malignant breast cells [146-148].

(13) Polymersome: Polymersomes are synthetic vesicles, small empty with a solution. These nanoparticles are made of amphiphilic synthetic block copolymers that shape the vesicle membrane and have sizes fluctuating from 50 nm to 5 μm [149].

Both hydrophilic doxorubicin hydrochloride (DOX·HCl) and hydrophobic doxorubicin base (DOX) can be delivered by polymersomes to the breast tumor cells [150].

Lipid Nanoparticles: (1) Solid lipid nanoparticles: Solid lipid nanoparticles (SLNs) have been produced to transport dissolvable water drugs and corrective dynamic medication efficiently. These NPs are made up of assembled quality polymers, making them capable of advanced drug delivery with less toxicity [151, 152]. Doxorubicin encapsulated in lipid nanoparticles (SLN-Dox) goes through the cell membrane via endocytosis and arrives at the cytoplasm. This drug-NP complex overcomes the resistance mechanism in the cell membrane without the support of a chemosensitizer [153, 154]. An examination that Bin Lu and Su-Bin Xiong did showed that conjugation of solid lipid nanoparticles with mitoxantrone could controllably release without burst effect and high effectiveness in the targeting of the drug to lymph nodes and a definite affinity for tumor

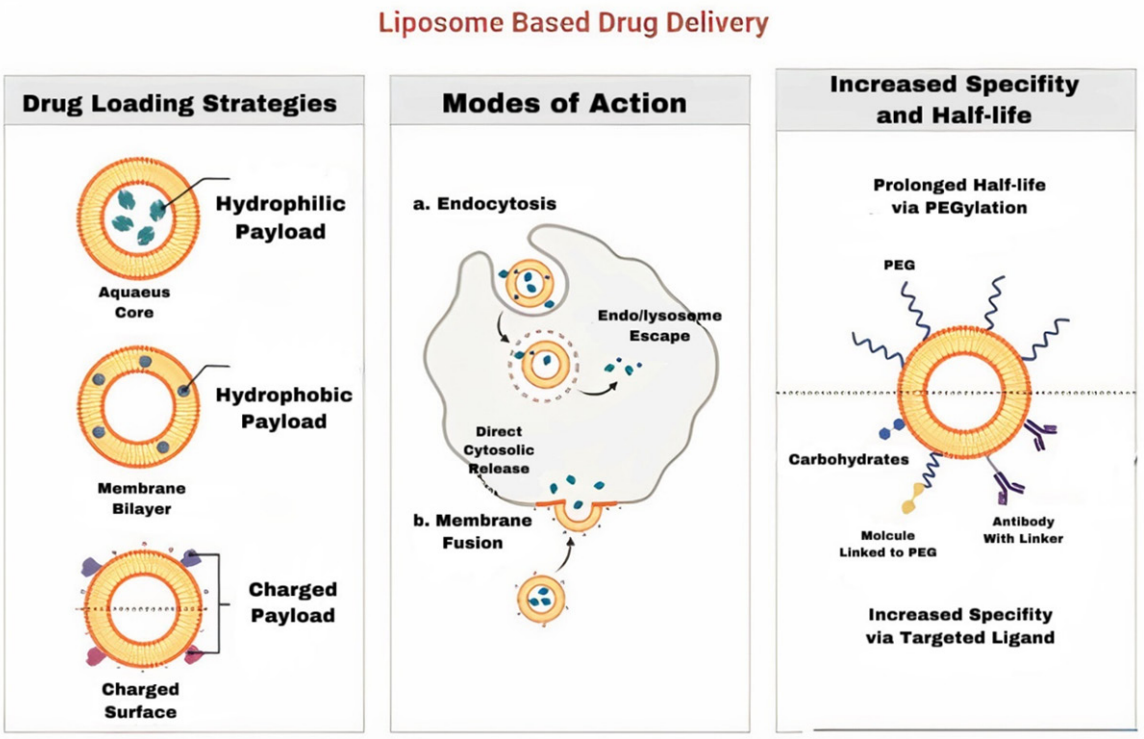

Figure 7. Liposomes are new drug delivery structures that have vesicular structures consisting of bilayers. These nanoparticles are made of aqueous spaces, which are surrounded by a membrane created of lipid bilayers.

tissues which assistances to improve the therapeutic outcome and diminish the side effects of anti-tumor agents [155]. In another examination that Oliveira da Rocha and Bento da Silva did show that a combination of solid lipid nanoparticles and Docetaxel can inhibit the tumor growth of 4T1 breast cancer; furthermore, it did not have noticeable systemic noxiousness in mice; consequently, it can be used for the treatment of breast cancer [156].

(2) Liposome delivery: Liposomes are spherical systems designed by one or multiple concentrical lipid bilayers surrounding separate aqueous spaces [157]. These NPs are usually manufactured with innately connected phospholipids, chiefly phosphatidylcholine. To amend the membrane's firmness and enhance stability, cholesterol is often manufacturing liposomes. The molecular load is filled via liposome formation in aqueous solution, solvent substitute mechanisms, or pH gradients techniques [158]. Indeed, liposomes are the most valuable and complex NP class because of their ability to carry numerous biologically effective complexes and macromolecules [159-161]. Liposomes have exclusive features for drug delivery; actually, they can include an extensive diversity of hydrophilic and hydrophobic diagnostic or therapeutic mediators (**Figure 7**) [162]. In eliminating tumor cells, liposomes have been established to be very practical. The purpose behind that is liposomes decrease the toxic side effects of chemotherapeutic medications and increase their anti-cancer effectiveness [163]. For progressive chemotherapy of tumor cells, size is the critical feature of liposomes; Bigger liposomes are efficiently eliminated from circulation by the reticuloendothelial system (RES) [164]. Liposome-based chemotherapeutics can gather in tumor tissue with this "passive" drug transport [165]. Metformin (MET), an antidiabetic drug, also has been effective against breast cancer. MET can be delivered to the tumor cells by MET-encapsulating liposome (LP-MET) and Herceptin-conjugated LP-MET (Her-LP-MET), which have shown promising results both in vivo and in vitro [166]. The Zeta potentials of LP-MET and Her-LP-MET and their size efficiently increase penetrability and retaining effects [167]. In the same way, PEGylated DSPC liposomes produced with the microfluidic

system containing doxorubicin expose less toxicity because of their sustained release from the liposome [168].

Inorganic nanoparticles and nanocrystals

Inorganic Nanoparticles and Nanocrystals are made of crystalline clusters of atoms (from just a few to numerous tens of thousands). When the size of the resources is decreased to the nanometer scale, their natural features can be extraordinarily altered, and novel physical features can appear [169]. Inert metals such as gold and titanium shape nanospheres; nevertheless, iron oxide nanoparticles similarly turn out to be a choice. Several latest findings, like the nanoparticles' intracellular degradation or the tight connection amid intracellular localization and local nanoparticle concentration and their cytotoxic consequence [170, 171], offer new visions to undertake the influence of nanoparticles on cells. Metal inorganic nanoparticle structures break down into their component metal atoms, and these materials might have contact with biosystems. A significant quantity of these nanoparticles might stay in the body after treatment which can cause toxicity [172]. Inorganic NPs have exclusive properties, which contributes to the lessening of nontoxic photosensitizer (PS) leakage, allow for a high loading capacity of PSs, augment PS passive uptake, and allow for ease of functionalization with numerous ligands to promote active PS absorption and, therefore, allow for the overall improvement of photodynamic treatment of breast cancer treatment [173-175].

Metal nanoparticles: Metal nanoparticles are micron-sized systems containing metals like gold, silver, titanium, platinum, cerium, zinc, thallium, and iron, or their composites like hydroxides, oxides, sulfides, fluorides, chlorides, and phosphates [176]. Noble metal nanoparticles (Ag, Au, Pt) are useful for numerous biomedical uses like anti-cancer, radiotherapy enhancement, drug transfer, thermal ablation, and many others [177]. Ionic covalent bonding and physical absorption can attach gold nanoparticles (AuNPs) surfaces to drugs that are transferred to the tissue and regulate drug release via biological stimuli or light initiation [178]. Noble metal NPs have exclusive features like high surface-to-volume ratio, vast optical components, effortless manufacturing, and trouble-free surface chemistry, making them versatile for cancer treatment [179-182].

(1) Gold nanoparticles: Gold nanoparticles (AuNPs) are small gold particles with a diameter of 1 to 100 nm, which, once distributed in water, are also acknowledged as colloidal gold [183]. Gold nanoparticles can be utilized to enhance the biodistribution of drugs to diseased organs, tissues, or cells to improve target drug delivery [184, 185]. Gold nanoparticles can accumulate in breast tumor tissue. Conjugated with drugs such as Trastuzumab, it can also be a drug carrier to augment uptake of the drug to the tumor tissue [186]. Sani A's studies have shown that AuNPs are not poisonous; nevertheless, many other studies oppose this declaration; consequently, further studies are needed [187]. In Libutti SK's experiment, a new nanomedicine was conjugated with human tumor necrosis factor-alpha (rhTNF) and thiolated PEG onto the surface of gold nanoparticles (named CYT-6091) [188]. The outcomes presented that it was less poisonous than treatment with only rhTNF. Moreover, the gold nanoparticles had accumulated in the tumor site and mostly avoided healthy tissue [189-191]. Zhang C's studies represented that by using the aptitude of doxorubicin to interpolate DNA duplexes, the novel dual-drug encompassing DNA-Gold nanoparticles, Dox@affi-F/AuNPs (dual-drug-containing affibody-DNA-Gold nanoparticles), can exhibit outstanding constancy in simulated physiological circumstances, and it could target HER2 overexpressing cancer cells [192]. Studies have revealed a prominent cytotoxicity outcome of prepared chrysin functionalized metal- reduced graphene oxide nanocomposites against breast carcinoma cells than the normal cells via prompting apoptosis, and it holds an optimistic future for cancer chemotherapeutic purposes; however additional studies need to be carried out with different types of cancer cell lines [193].

(2) Silver nanoparticles: Silver nanoparticles are nanoparticles of silver between 1 nm and 100 nm in size. While frequently described as 'silver', some are manufactured of a large percentage of silver oxide due to their large surface to bulk silver atoms [194]. Silver nanoparticles transport breast cancer drugs due to their competent agents targeting tumor cells and risk-free, healthy tissues [195]. Swanner and Fahrenholtz's examination for the first time

showed that systemically administered AgNPs effectively reduce the growth of solid, TNBC mammary tumors in mice, which supports the likelihood that AgNPs may be beneficial for the treatment of some human breast cancers [196].

(3) Platinum nanoparticles: Platinum nanoparticles are frequently in the form of a suspension or colloid of nanoparticles of platinum in a fluid, usually water [197]. Examination of Manzoor and Junaid Bashir showed that platinum nanoparticles also revealed anti-metastatic potential on the breast cancer cell. In the cell cycle analysis, platinum nanoparticles stimulated cell cycle arrest at the G0/G1 phase. Platinum nanoparticles also showed antibacterial properties against pathogenic bacteria [198].

Carbon nanotubes: Carbon nanotubes (CNTs) have become widespread and extensively investigated in medical use. They have proven to be effective in the areas of drug transport and biosensing techniques for cancer treatment. This method has been revealed to improve drug transport and biosensing techniques, and therefore, carbon nanotubes have lately drawn attention in cancer treatment [199]. CNTs are round unified cylinders of graphene layers, exhibiting distinctive physical, mechanical, and chemical features that have recently appealed to great attention [200-205]. Some evidence indicates that IGF1 (Insulin-like growth factor-1) and HER2-specific monoclonal antibodies can be attached to single-wall carbon nanotubes, which is a considerable step to overcome breast cancer in the late stages [206]. The field of carbon nanomaterials is developing technology with promising applications in the biomedicine field, especially for detecting, recognizing, and treating breast cancer. Nevertheless, no carbon nanomaterial simultaneously presents the desirable traits for therapeutic Administration in humans, and further studies are needed [207]. A novel treatment of metastatic breast cancer is also given by combining two advanced methods, including selective near-infrared photothermal removal and carbon nanotubes loaded with immune checkpoint inhibitors [208]. More specifically, this treatment uses anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) checkpoint inhibition, resulting in unrestrained T-cell propagation [209].

Ceramic nanoparticles: Ceramic nanoparticles (CNs) are developing as drug delivery systems, primarily because of their small size (<50 nm) and physicochemical features. They include albumin, iron oxide, or silica [210, 211]. Aluminum oxide (Al_2O_3) and titanium dioxide (TiO_2) are the most frequently used NPs for the proposal of nanocarriers. These NPs are not susceptible to swelling or variations in porosity with pH. Because of their more unchanging, bioavailable, readily makeable, and acceptable proteins and polypeptide formulation, ceramics nanoparticles are a particular carrier for protein and peptide delivery systems [212-214]. Based on the examination of Mahidhara and K Kanwar, they showed that iron-saturated-bovine lactoferrin-loaded alginate-enclosed chitosan-calcium phosphate (ACSC) ceramic Nano Capsules (Fe-bLf-loaded ACSC NCs) has promising anti-breast cancer efficacy in both in vitro and in vivo studies. The NCs proved to be highly anti-tumorigenic since none of the mice injected with breast cancer cells developed tumors in the xenograft models [215].

Nanoparticle albumin-bound (nab) technology

Paclitaxel (nab-paclitaxel; Abraxane®) is Food and Drug Administration-approved nanoparticle albumin-bound (nab™) for curing metastatic breast cancer. The key feature of the drug is that the formulation has no conventional surfactants in water-based injections [216]. Albumin is a versatile biomaterial for the manufacturing of NPs [217]. The effectiveness of the albumin-based transfer exists in its capability to boost tumor targeting and accumulation. For example, improved tumor accumulation is due to the enhanced uptake passively facilitated by the improved permeability and retaining effect [218].

Human serum albumin (HSA) nanoparticles

Prepared human serum albumin (HSA) can be used as one of the versatile carrier structures for drug delivery [219]. HSA nanoparticles can bind to numerous drug molecules and have excellent stability during storing and in vivo applications. Also, the toxicity and antigenicity of these NPs are very low. Biodegradability, reproducibility, and manageable release are other significant features of HSA nanoparticles. In addition, due to the numerous drug bind-

Table 3. Monoclonal antibody especially for breast cancer

Drug	Mechanism	Type	Therapy Group	Side effects	FDA Approval	REF.
Pertuzumab	HER2/neu	Humanized monoclonal antibody	Metastatic HER2-positive breast cancer	Risk of infection, Bruising and bleeding, Anemia, Diarrhea, Loss of appetite, Sore mouth	Yes	[244]
Trastuzumab	HER2/neu	Humanized monoclonal antibody	breast cancer and stomach cancer	flu-like symptoms (high temperature, chills, and mild pain), nausea, and diarrhea	Yes	[245]

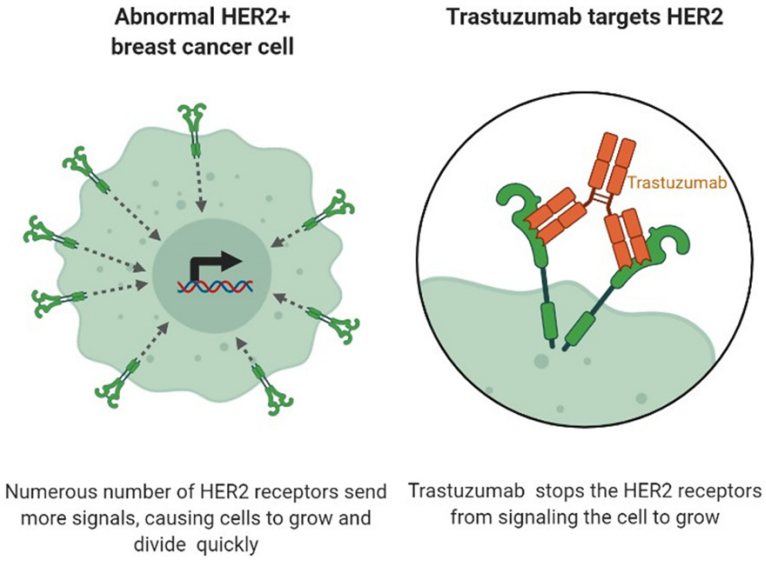

Figure 8. Mechanism of trastuzumab.

ing sites on the albumin molecule, significant amounts of drugs can be loaded on the matrix of HSA nanoparticles [220, 221].

Antibody monoclonal modified-nanoparticles

Monoclonal antibodies (mAbs) are produced by B cells and specifically target antigens [222]. Pertuzumab and Trastuzumab are the most favorable and Food and Drug Administration approved antibodies used in breast cancer treatment, and they target HER2/neu receptors and inhibit cell growth rate [223, 224] (**Table 3**; **Figure 8**). HER2 is a receptor with tyrosine kinase activity and participates in the epidermal growth factor receptor family [225] (**Figure 9**). HER2 is highly expressed in around 20-30% of breast cancer tumors, and the outcome of that is a more aggressive ailment, augmented mortality, and higher recurrence rate [226]. NPs containing HSA show a promising approach for targeted drug delivery to tumor cells; consequently, the binding of HSA nanoparticles to the antibody trastuzumab takes advantage of the capability of HER2-positive cells to integrate elements binding to HER2, and it is an appropriate method for treatment [227]. Conjugation of antibodies with nanoparticles such as gold, metal, iron oxide with different sizes and shapes showed promising results in Bryan E. White and Molly K. White's examination [228].

Discussion

Breast cancer is one of the foremost causes of death among women; subsequently, immunologists worldwide are trying to treat this problem. One of the best cures for treating this malignancy is nanoparticles and monoclonal antibodies. Her2/neu is a receptor that is in charge of breast cells' growth every single cell by sending signals to nuclear cells; however, in some tumoral cells, it overexpresses; thus, cells begin to grow uncontrollably. The advent method of utilizing nanoparticles to treat cancer has significantly changed the protocols for eliminating tumor cells and drug delivery. The most significant advantage of these nanoparticles is precise targeting in which the drug does not affect other healthy tissues and just attacks the malignant cells. Also, drugs carried in nanoparticles are more stable than other conventional drugs and are protected from degradation or environmental effect. Biocompatibility, or fewer side-effects, is another advantage of these nanosized particles used as drug transporters. This means that these materials are compatible with living tissue, and we experience fewer second-

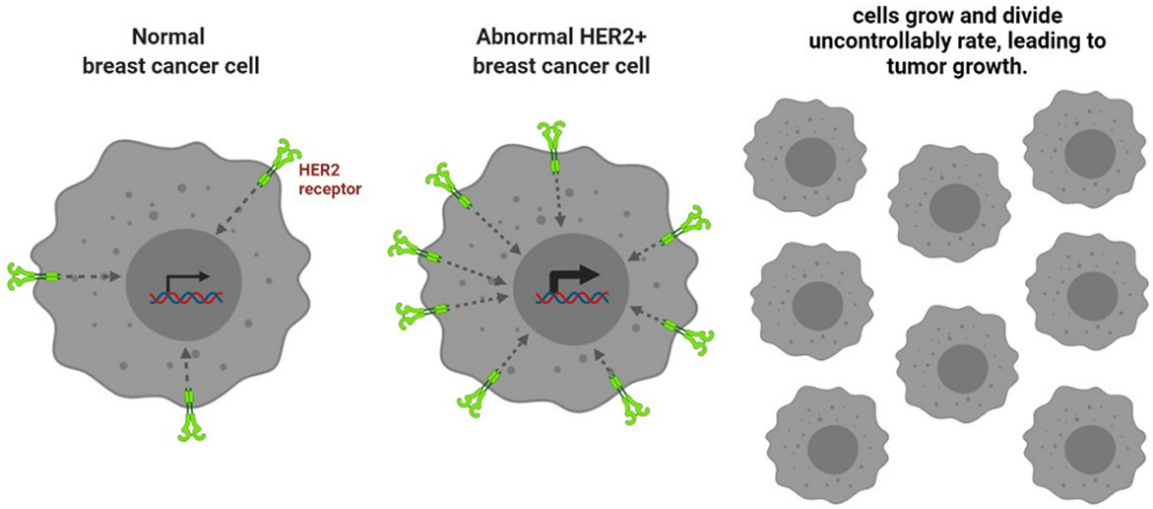

Figure 9. HER-2 receptors send signals to cells and are in charge of cell growth; thus, in breast cancer, it causes cells to grow and divide at an uncontrolled rate, leading to tumor growth. Arrows in the figure illustrate growth signals from HER2 receptors to the nucleus of cells.

ary adverse effects other than the therapeutic influence.

Due to the fact that breast cancer is one of the invasive types of cancers, especially among women, the classification of nanoparticle usages and their results can assist in remedying the treatment of this malignancy. Countless nanoparticles have been developed to eradicate breast cancer; however, no article clearly classified them. Therefore, this article has tried to gather all valuable data to this extent. The name of nanoparticles, their results, and their future function have been mentioned to assist physicians and scholars remedy this cancer.

All in all, these benefits have made nanoparticles one of the most valuable tools to cure cancer. Every nanoparticle has its exceptional characteristic, but Among NPs, due to their unique features and fewer disadvantages, polymeric NPs and compact lipid nanostructures like phospholipids, including liposomes and micelles, seem to be the best choice in drug transport to breast cancer cells. Liposomes can carry a wide variety of biologically active compounds because of their high firmness and stability that keep these compounds safe. With fewer side effects, greater-sized liposomes are also an excellent choice for drug delivery since they are removed faster through the reticuloendothelial system (RES). Polymeric nanoparticles, specifically PCL, PEG, nanospheres, and nanocapsules, tend to be ideal drug transporters to the targeted breast tumor cells. Again, outstanding stability is why these NPs are widely utilized in drug delivery systems. Various bioactive drugs make them sufficient drug transporters since they guard medications against biodegradation and enzyme effects. For battling these tumoral cells, some drugs can be used to target these receptors, and by blocking those signaling, tumoral cells begin to diminish. Compared with other monoclonal antibodies such as PD-1 inhibitors, Her2/neu Mabs give promising and better outcomes. The FDA-approved monoclonal antibody for this kind of treatment is Pertuzumab and Trastuzumab, which explicitly targets Her2/neu receptors. These two monoclonal antibodies are humanized; subsequently, the body does not battle against them, and it does not assume them as an unknown substance so that they can be used safely; however, they have some adverse effects; therefore, the physician should pay attention to patients' overall stability for prescribing those for patients' therapy. Some of those side effects are the risk of infection, bruising and bleeding, Anemia, Loss of appetite, Sore mouth, flu-like symptoms (such as fever, chills, and mild pain), nausea, and diarrhea. Besides, most Nps cannot be administrated in clinical stages, so exploring possible methods to make them clinically applicable is the main challenge for future research. For the

first time, this article discussed the most novel method to treat breast cancer in the most effective way possible by gathering recent data from numerous nanoparticles and breast cancer immunotherapy articles.

Conclusion

Nanoparticles are designed to improve the qualities of conventional drugs, especially chemotherapeutic agents, in numerous aspects. These nanocarriers hinder the degradation of the drug, decrease toxicity and adverse side effects and control the sustained release of the medication. Breast cancer is also treated with these versatile nanocarriers, exclusively Polymeric NPs, in the most efficient way possible. Although abundant nanocarriers have been investigated preclinically, only a handful of nano carrier-based drugs such as Doxil (Caelyx) (Liposomal Doxorubicin (PEGylated)), Myocet (Liposomal doxorubicin (non-PEGylated)), Lipusu (Liposomal paclitaxel), and Abraxane (Albumin-particle bound paclitaxel) are approved by Food and Drug Administration (FDA) and available in the pharmaceutical market for treating breast cancer in different stages. However, most of these NPs are still in vivo and in vitro stage and do not have clinical use, so there are no clear clinical records for most of the NPs.This review illustrates that much work must be done to discover new methods to clinically utilize the NPs and manufacture more efficient and less toxic drugs. This article highlights the advantages and drawbacks of all available NPs and opens the gates for further investigations by reviewing the most prominent studies in this field.

Disclosure of conflict of interest

None.

Abbreviations

NP, Nanoparticles; ER, Estrogen receptor; HER2, Human epidermal growth factor receptor 2; PgR, Progesterone receptor; MPs, Microparticles; PLGA, Poly lactic-co-glycolic acid; NNI, National Nanotechnology Initiative; EPR, Enhanced permeability and retention; PEG, Polyethylene glycol; PCL, Poly-ε-caprolactone; PCL-PEG, polycaprolactone-polyethylene glycol; EGFR, Epidermal growth factor receptor; TNBC, Triple-negative breast cancer; DOX, Doxorubicin; CSeSiO2 HNPs, pH-sensitive chitosan silica hollow nanospheres; Erb2, Erythroblastic oncogene B; AG, Amphiphilic gelatin; CaP, Calcium phosphate; PLA, Polylactic Acid; PTX, Paclitaxel; HCN, Hollow carbon nanospheres; PAMAM, Polyamidoamine; TZ, Trastuzumab; DTX, Docetaxel; NIR, Near-infrared; TPGS, Tocopheryl polyethylene glycol succinate; TOS, Tocopheryl succinate; DOX·HCl, doxorubicin hydrochloride; SLN, Solid lipid nanoparticles; RES, Reticuloendothelial system; PS, Photosensitizer; CNT, Carbon nanotubes; IGF1, Insulin-like growth factor-1; CN, Ceramic nanoparticles; Fe-bLf-loaded ACSC NCs, Iron-saturated-bovine lactoferrin-loaded alginate-enclosed chitosan-calcium phosphate ceramic Nano Capsules; HSA, Human serum albumin; mAbs, Monoclonal antibodies; Dox/F127&P123-Tf, a transferrin (Tf)-conjugated polymeric nanoparticle composed of poloxamer 407 (F127) and 123(P123); DTX/Apt-pD, docetaxel/aptamer-polydopamine.

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