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REVIEW

Research Progress of Docetaxel Nano-Drug Delivery System in the Treatment of Breast Cancer

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Abstract: Breast cancer (BC) is the most common malignant tumor in women. Docetaxel (DTX), a chemotherapeutic agent derived from paclitaxel (PTX), has received approval from the US Food and Drug Administration (FDA) for the treatment of BC and various other malignancies. Nevertheless, its utility in clinical settings is constrained due to its poor water solubility and low oral bioavailability, dose-dependent toxicity, and a short systemic circulation half-life. Developing nano-drug delivery systems for DTX represents a well-established strategy to overcome these limitations. This review, based on a literature search of the PubMed database from 2019 to 2024 using the keywords "docetaxel", "breast cancer", and "nano-drug delivery system", summarises recent advances in targeted nanomedicine delivery systems for DTX and their application in BC treatment when combined with other delivery therapies. Nano-drug delivery systems encompass passive targeting (such as: nanomicelles, liposomes), active targeting (such as: G protein-coupled oestrogen receptor, integrin protein receptor), physicochemical targeting (such as: magnetic-responsive, temperature-responsive), and combined delivery (such as: photothermal therapy, chemotherapeutic drugs, and active components of traditional Chinese medicine). These systems hold great promise for enhancing DTX bioavailability, improving tumor targeting, and regulating drug release. Furthermore, key challenges limiting clinical translation are analysed. This paper provides a theoretical foundation and practical guidance for rationally designing DTX nanomedicines, accelerating their transition from laboratory research to clinical application and offering new hope for BC treatment.

Keywords: breast cancer, docetaxel, passive targeted, active targeted, physicochemical targeted, co-delivery

Introduction

So far, cancer is still one of the major diseases that threaten human life and health. According to the World Health Organization, there will be nearly 20 million new cancer cases and 9.7 million deaths worldwide in 2022. The incidence of breast cancer (BC) in women is second only to lung cancer, accounting for 11.6% of the total number of global cancer cases,[1] which is the leading type of malignant tumor affecting women's health.[2] Currently, there has been a gradual trend of breast cancer becoming younger, with approximately 7-10% of young patients being diagnosed with BC.[3] According to data released by the International Agency for Research on Cancer (IARC), the global prevalence of BC is rising annually in the majority of regions across the globe.[4] In addition, based on molecular and histological characteristics, BC can be categorised into three subtypes, with treatment strategies exhibiting significant differences across these subtypes: (1) BC expressing hormone receptors (estrogen receptor positive (ER+) or progesterone receptor positive (PR+)) is mainly treated with endocrine therapy, and some high-risk patients need to add chemotherapy; (2) BC expressing Human Epidermal Growth Factor Receptor 2 (HER2+). The treatment strategy for this type of BC focuses on the organic combination of chemotherapy and targeted therapy, which improves the effectiveness and targeting of the treatment by precisely hitting the cancer cells; (3) Triple-negative breast cancer (ER-, PR-, and HER2-), which currently relies on chemotherapy for clinical intervention but has relatively limited therapeutic effects.[5,6] Currently, the common treatments for BC include chemotherapy, endocrine therapy and radiotherapy. Among them, chemotherapy is the most dominant

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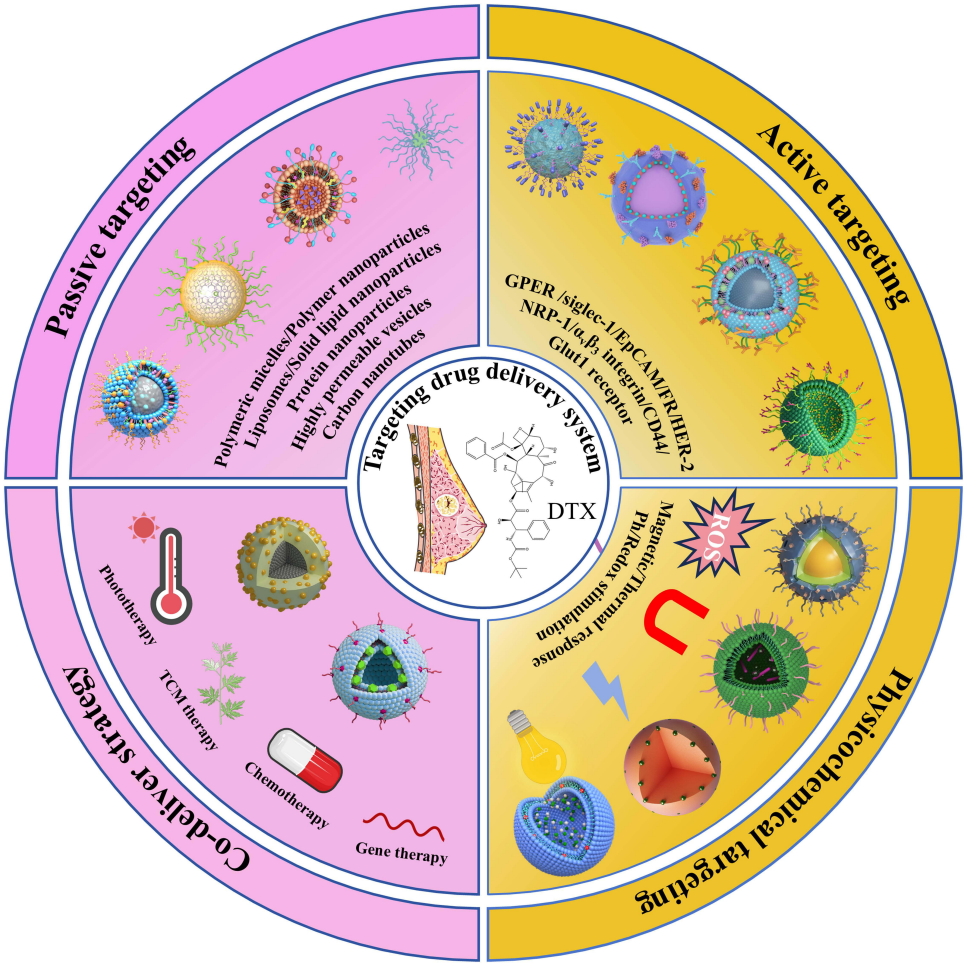
Graphical Abstract



treatment for BC, but most chemotherapy drugs suffer from the drawbacks of being highly invasive and lacking tissue specificity, readily causing toxic side effects in normal tissues such as the digestive, haematological, and nervous systems. This severely impacts patients quality of life and, to a certain extent, limits their clinical efficacy.[7]

The main chemotherapeutic agents used in the treatment of BC are PTX, DTX and Gemcitabine (GEM).[8] In particular, PTX-based chemotherapeutic agents are often used as one of the preferred treatment options for women with early or locally advanced BC.[9] DTX ($C_{43}H_{53}NO_{14}$) is currently the first-line drug in PTX-based anti-breast cancer treatment, originally extracted from the needles of the European sequoia (Picea abies) and later made by artificial semi-synthetic technology, it is a sequoia chemical with important medicinal value. In 1996, it was approved for marketing by the United States FDA.[10] The main functioning mechanism of DTX is to bind to the β-microtubule protein of cells, enhance the formation of microtubules from microtubule proteins and hinder their normal depolymerisation, interfering with the functioning of microtubule bundles and preventing the formation of spindle filaments and spindle bodies during mitosis, and stagnating in the G_2 and M phases, which leads to the death of the tumor cells.[11] Previous studies reported that DTX is more advantageous than PTX, and the mechanism of cytotoxic action of DTX is the same as that of PTX, but DTX hinders microtubule depolymerisation and enhances microtubule formation by microtubule dimer twice as much as that of PTX, and also has higher tumor-suppressing activity than PTX in vitro, and anti-tumor activity about twice as much as that of PTX.[12] Moreover, in clinical applications, DTX is a more promising inhibitor of cellular microtubule

proteins due to its shorter intravenous administration time, less allergic reactions and toxicity compared to PTX. In addition, DTX has been shown to be therapeutically superior to PTX in some clinical trials and is even able to be used as an active molecule alone for the treatment of metastatic breast cancer. However, DTX is a highly lipophilic drug, and this property leads to its extremely low water solubility and poor stability, which greatly limits its therapeutic efficiency. In the actual delivery process, the efficacy of this chemotherapeutic drug is limited by various factors. In addition, its distribution in normal tissues and organs is not ideal, which can lead to a series of adverse reactions and toxic side effects,[13,14] such as nausea, vomiting, alopecia, decreased immunity and a series of other adverse reactions, which seriously affects the patient's adherence. How to overcome the physicochemical defects of DTX and optimize targeted delivery has become a key challenge to enhance its clinical application value.

To address these issues with DTX, a variety of DTX formulations have been introduced to the market, each with unique features and benefits, as well as different challenges (Table 1). The conventional solvent-based formulations are dissolved in Tween 80 and ethanol to increase their solubility.[15] However, due to the side effects of Tween 80, various adverse reactions occur in the body,[16] such as nausea, hair loss, neutropenia, allergic reactions, fluid retention, etc,[17] which seriously threaten the health of patients,[18] and greatly limit the application of these preparations in clinical treatment. A nanosomal lipid suspension of DTX (marketed as DoceAqualip® in India) has been approved for the treatment of BC. Using nanoparticle technology, it achieves a certain degree of drug accumulation at the tumor site through the enhanced permeability and retention (EPR) effect.[19] Nanoxel M is an injectable docetaxel polymer micelle with mPEG-b PDLLA as the active ingredient carrier. Compared to existing formulations, it exhibits passive tissue targeting and synergistic efficacy with reduced toxicity, whilst also avoiding adverse effects such as allergic reactions and fluid retention associated with current preparations, thereby offering enhanced clinical safety. However, the polymeric carrier may induce injection site reactions (such as pain and inflammation), and long-term in vivo metabolic data remain insufficient, with potential accumulation risks yet to be fully elucidated. In addition, the new drug BH009 (trade name: BEIZRAY®) has made a major breakthrough in formulation development by using the marketed human albumin for intravenous infusion as a carrier, without adding any new excipients to avoid additional safety risks. BH009 not only

Table 1 Docetaxel Product Information

Trade Name	Auxiliary Ingredients	Indications	Year
Taxotere®	Tween 80; ethanol.	Locally advanced or metastatic breast cancer and non-small cell lung cancer.	1995
Duopafei®	Tween 80; ethanol; Citric acid.	Locally advanced or metastatic breast cancer and non-small cell lung cancer.	2003
Docefrez®	Tween 80; ethanol.	Breast, lung, prostate, stomach and head and neck cancers.	2011
Nanoxel M	mPEG-b PDLLA.	Ovarian cancer, breast cancer, non-small cell lung cancer, prostate cancer, pancreatic cancer, gastric cancer, oesophageal cancer, soft tissue tumors, head and neck tumors.	2012
DOCETAXEL	Tween 80; ethanol; sterile water for injection.	Advanced breast cancer, ovarian cancer, non-small cell lung cancer.	2012
DoceAqualip®	Soy phosphatidylcholine; sodium cholesteryl sulfate.	Advanced gastric adenocarcinoma, breast cancer, testicular cancer, non-small cell lung cancer.	2013
DOCETAXEL	Tween 80; ethanol; sterile water for injection.	Advanced breast cancer, ovarian cancer, non-small cell lung cancer.	2017
DOCETAXEL	Tween 80; ethanol; sterile water for injection.	Advanced breast cancer, ovarian cancer, non-small cell lung cancer.	2021
BEIZRAY®	Human albumin.	Breast, non-small cell lung, squamous head and neck, prostate and stomach cancers.	2024
DOCETAXEL	Tween 80; ethanol; sterile water for injection.	Advanced breast cancer, ovarian cancer, non-small cell lung cancer.	2024

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effectively eliminates the serious side effects caused by the addition of Tween 80, but the breakthrough application of this solubilisation technology also makes the incidence and severity of haematotoxicity (such as lowering of neutrophil counts, lowering of white blood cell counts, etc) of BH009 significantly reduced, and the overall safety is better than that of the currently marketed DTX products.

Although a variety of DTX preparations have been used in the treatment of breast cancer and have achieved certain results, the effect of these preparations in vivo is often restricted by many factors, among which tumor microenvironment (TME) is one of the core influencing factors. As a complex internal environment for tumor cell growth, TME is composed of tumor cells, immune cells, mesenchymal stromal cells and extracellular matrix (ECM). Its unique physical and chemical properties (hypoxia, acidic pH, high interstitial fluid pressure) and biological barrier effect greatly reduce the delivery efficiency of drugs to tumor tissues.[20] BC, as a type of solid tumor, has typical biochemical and biophysical features, including high mesenchymal pressure, dense mesenchymal tissue, and complex interactions with macrophages, fibroblasts and tumor cells.[21] These features lead to a growth-induced stress response that acts as a biological barrier, further limiting the penetration of nanoparticles into the tumor parenchyma after extravasation from the vasculature, thus reducing the efficiency of nanoparticle delivery.[22] In addition, the acidic microenvironment generated by anaerobic glycolytic metabolism of malignant tumors is not only an important driving factor for tumorigenesis, invasion, metastasis and drug resistance, but also a key condition for BC cells to adapt to harsh environments and maintain survival. At the same time, the hypoxic state and non-cellular components such as ECM in TME can also hinder the role of drugs at the molecular and structural levels by activating hypoxia-inducible factor transcription, accumulating lactic acid, and building physical barriers. In BC, tumor-associated macrophages (TAMs), as the largest number of mononuclear phagocytes, further aggravate the difficulty of drug delivery by releasing a variety of cytokines to mediate angiogenesis, drug resistance and metastasis. Therefore, by adjusting and modifying these properties of the TME, a more efficient drug delivery system can be designed to overcome the barriers to drug delivery and improve therapeutic efficacy.

Through in-depth research and precise grasp of these complex characteristics of the TME, and targeted adjustments and changes to it, it is expected to design a more efficient and precise drug delivery system, thus breaking through the current dilemmas faced by tumor therapy and improving the effectiveness of tumor treatment. Nano-drug delivery systems have demonstrated numerous benefits in oncological therapy, helping to improve the stability of the drug, its solubility in water, the time it circulates in the blood, the controlled release and the targeted delivery of the drug to the tumor site.[23] Targeted delivery of nanomedicines is primarily categorised into passive and active targeting, which share both commonalities and distinctions in their mechanisms and applications (Figure 1). Passive targeting is achieved by regulating nanoparticle size, optimising surface loading, and employing coatings for spatial stabilisation. Drug delivery relies primarily on the EPR effect-a phenomenon facilitated by loose junctions in tumor vascular endothelial cells, high vascular permeability, and reduced lymphatic drainage. This enables passive leakage of nanocarriers through blood vessels to reach tumor sites.[24] Although nanoparticle drugs have demonstrated preferential accumulation in mouse tumor models via the EPR effect, their performance in patients remains unclear, and most currently approved nanoparticle drugs still rely on passive targeting capabilities. Active targeting can be achieved by grafting corresponding ligands or antibodies onto nanocarriers to precisely recognise overexpressed receptors or antigens on cell surfaces. Following extravasation, the nanocarriers can accumulate within tumor tissue and undergo internalisation via receptor-ligand (or antigen-antibody) specific recognition. A small number of nanocarriers capable of ligand-mediated active targeting are also being investigated in clinical trials. However, clinical outcomes indicate limited efficacy gains from ligand-mediated targeting strategies (compared to non-ligand nanoparticles), likely due to protein coats shielding surface ligands. Numerous studies confirm the EPR effect as the foundation for active targeting, requiring nanoparticles to overcome multiple biological barriers and leverage favourable EPR effect to reach tumors and activate ligand-mediated targeting. Physicochemical drug delivery systems represent another compelling avenue in pharmaceutical delivery. These innovative systems enable spatially and temporally controlled drug release in response to diverse stimuli, including pH, temperature, enzymes, oxidative stress, magnetic fields, light, ultrasound, and heat. By responding to specific internal or external triggers, these nanocarriers can mitigate side effects associated with encapsulated therapeutics, thereby enhancing patient compliance.[25,26] In addition, co-delivery of drugs through the same vehicle can achieve synergistic effects through simultaneous exposure of drugs in the tumor and in the cells, thus enhancing efficacy and reducing adverse effects.[27]

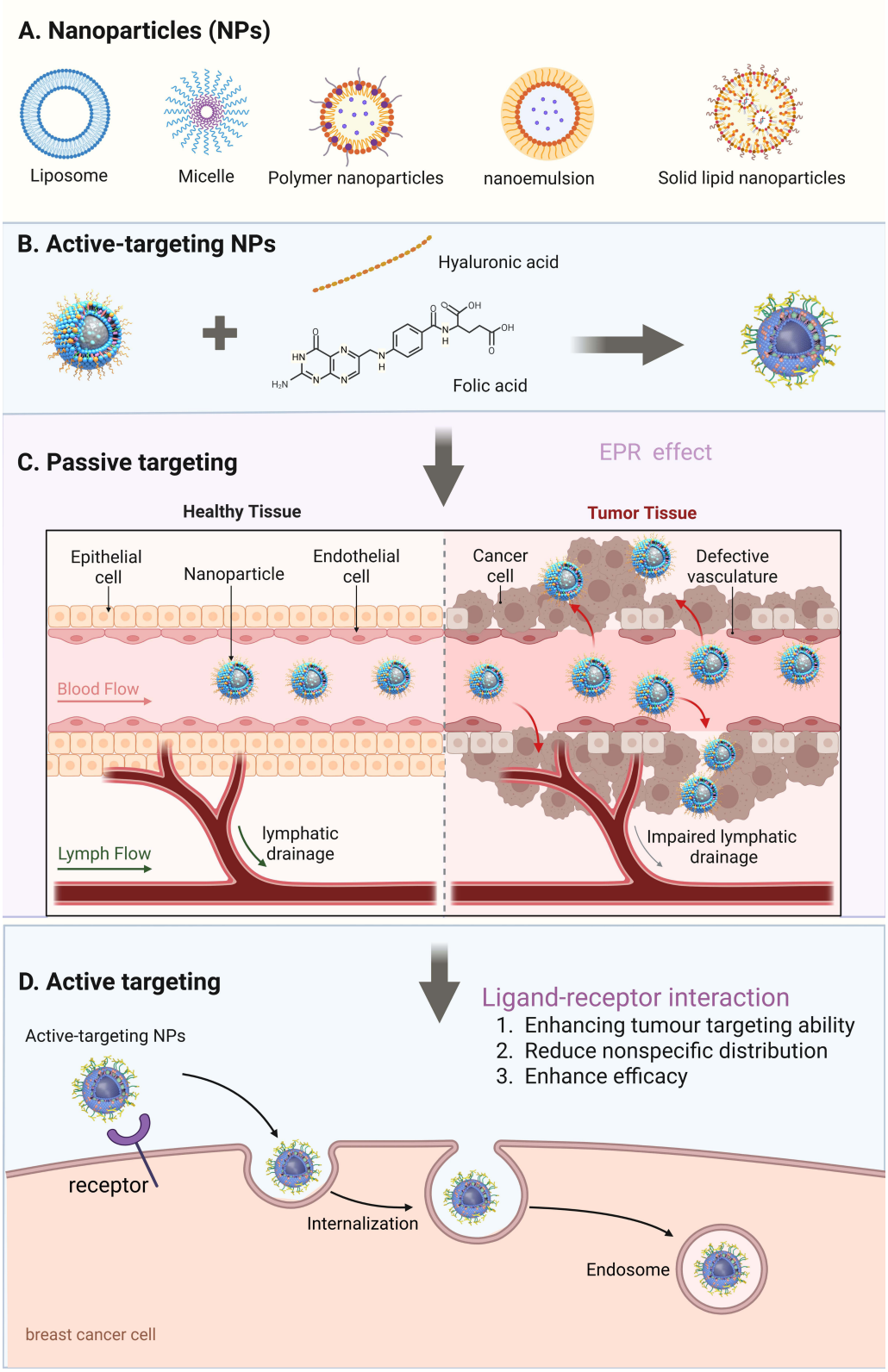

Figure 1 The integrated schematic diagram of active and passive targeting mechanisms: (**A**) Nps drug delivery platforms; (**B**) Construction of actively targeted Nps; (**C**) Passive tumour targeting via the EPR effect; (**D**) Active tumour targeting through ligand-receptor interactions. Created in BioRender. (https://BioRender.com/nffm1ua).

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With the deepening of research and continuous technological advances, the delivery routes of DTX formulations have been further expanded. Different routes of administration provide more feasible options for nanomedicine delivery, effectively improving bioavailability and active targeting ability, thus enhancing efficacy and avoiding first-pass metabolism.[28] More precisely, parenteral routes (such as intravenous, intramuscular, or subcutaneous administration) and certain mucosal routes (such as nasal, pulmonary) bypass hepatic first-pass metabolism, whereas oral administration typically does not. In recent years, with the development of nanotechnology, various novel DTX nano-delivery system, such as polymeric micelles, liposomes, nanoparticles, and nanoemulsions, have been reported to be successfully used for targeted therapy of BC. These innovative drug delivery systems have brought about significant enhancements. They have notably increased the bioavailability of DTX, effectively slowed down the drug's release rate within the body, remarkably enhanced the drug's ability to target tumors. However, existing research has predominantly focused on optimising individual systems, lacking a systematic comparison of how different nanocarrier structures influence the in vivo fate of DTX. Consequently, this paper presents an all-encompassing summary of the research regarding the integration of targeted drug delivery systems with DTX. On one hand, it classifies targeted delivery systems based on mechanisms (passive targeting relying on EPR effect, active targeting via receptor-ligand interaction, physicochemical targeting responsive to tumor microenvironment pH/temperature), and critically analyzes their advantages and limitations in BC therapy; on the other hand, it systematically combs co-delivery systems of DTX with photothermal therapy, traditional Chinese medicine active ingredients, chemotherapeutic agents, and gene therapy. The unpredictable behaviour of nanoparticles within complex human systems continues to pose challenges in translating nanotechnology and biomaterials research into clinical applications, particularly within the field of nanomedicine. Preclinical models frequently fail to predict human outcomes, immune responses, or disease variability, especially in cancer and complex therapeutic regimens.[29] Therefore, this paper provides a unique and systematic summary of the comprehensive research on DTX-targeted drug delivery systems and the challenges in their clinical translation, offering more practical guidance for the development of clinical DTX nanomedicines (Figure 2).

Passive Targeted Drug Delivery System

Passive targeted drug delivery system is a targeted therapy that utilises the structural characteristics of specific tissues and organs to naturally distribute the drug to the lesion site. EPR effect result in the accumulation of nanoparticles in cancerous tissues more than in normal tissues, as the differences between the vasculature of tumor tissues and that of normal tissues allow drug carriers with a nano-size of tens to hundreds of nanometres to leak out of the vasculature and into the tumor tissue more easily.[30] Common carriers for passively targeted agents include nanomicelles, liposomes, nanoparticles, and nanoemulsions. The key characteristics of these systems have been summarized in Table 2.

Polymer Micelles

Polymeric micelles such amphiphilic macromolecules are usually composed of diblock or triblock copolymers, which have both pro-solvophilic and hydrophobic blocks.[53] Among them, the hydrophilic head controls the drug metabolism process in vivo and protects the drug molecules from degradation or excretion. The hydrophobic core can encapsulate insoluble drugs and provide a suitable microenvironment for them and enable their stable and sustained release in vivo, thus effectively improving their bioavailability and therapeutic efficacy. Alshamrani et al[31] used two amphiphilic polymeric surfactants, chemical castor oil 40 (HCO-40) and D-α-Tocopherol polyethylene glycol 1000 succinate (VIT E TPGS), to prepare DTX nanomicellar formulation with an average particle size of 13.42 ± 0.62 nm and an encapsulation efficiency of 99.30 ± 1.96%. In vitro cytotoxicity studies showed that DTX nanomicelles exhibited higher anticancer activity against BC cells line (MCF-7) compared to natural drugs. However, the study validated efficacy solely at the MCF-7 cell level without establishing a tumor-bearing animal model. Consequently, it was unable to assess the in vivo distribution of nanomicelles or their tumor-suppressing effects. Furthermore, pharmacokinetic parameters were not measured, precluding determination of their circulation duration and metabolic pathways within the body. Lu et al[32] prepared DTX-loaded polymeric micelles (DTX PMs) and achieved a high encapsulation rate of 89%, prolonging the release time of DTX and enhancing its bioavailability. In addition, DTX PMs demonstrated a marked increase in in vitro cytotoxicity and the rate of cellular uptake compared to free DTX, and also exhibited higher antitumor activity [tumor

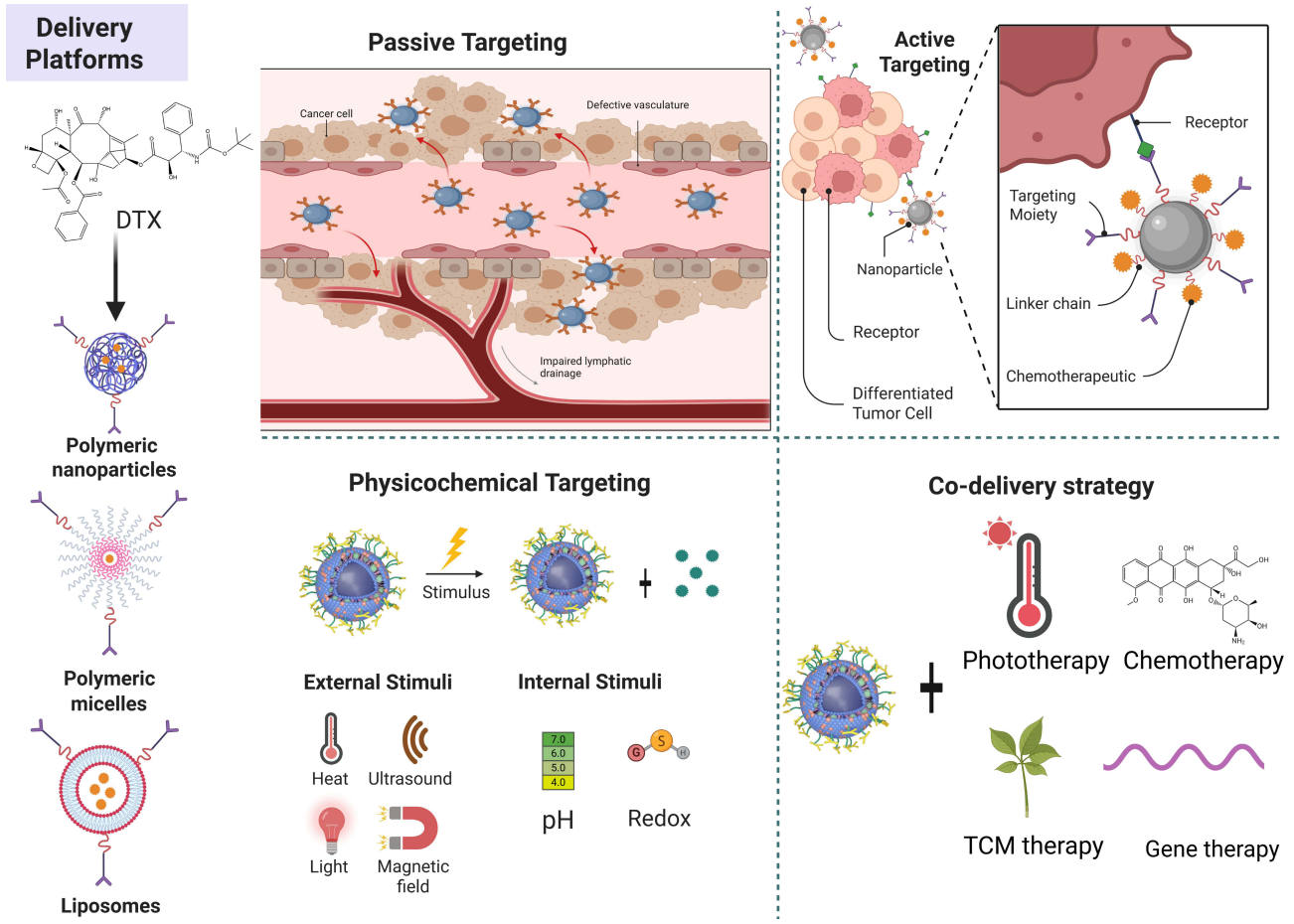

Figure 2 The classification diagram of NDDS based on DTX in the treatment of BC. Created in BioRender. (https://www.biorender.com/b7ij9aw).

inhibition rate (TIR): 67.19%]. Sreekanth et al[33] developed a supramolecular nanomicelle system based on the conjugate of PEGylated lithocholic acid (LCA) and DTX (LCA-DTX-PEG NMs). LCA-DTX-PEG NMs showed an increase in mean blood concentration (C_0) and area under the curve (AUC). LCA-DTX-PEG NMs showed high cytotoxicity to 4T1, MCF-7 and MDA-MB-231 breast cancer cells. Following treatment with LCA-DTX-PEG nanomaterials, tumor volume decreased and the number of metastatic nodules in the lungs was reduced in 4T1 tumor-bearing mice.

Table 2 Passive Targeting Drug Delivery System for DTX

Drug Delivery System	Ingredients	Characterization	Pharmacokinetics/TissueDistribution/Efficacy	Year, Refs.
DTX Polymer nanomicelles	HCO-40, VIT E TPGS.	Mean Size: (13.42 ± 0.62) nm Zeta potential: −0.19 mV EE: (99.30 ± 1.96) % DL: (3.62 ± 0.11) %	Apoptosis rate of MCF-7cells↑.	2022[31]
DTX Polymer nanomicelles	Mpeg 2kb-TRIA.	Mean Size: (93.7 ± 1.5) nm PDI: 0.212 ± 0.004 EE: (89.87 ± 3.45) % DL: (6.66 ± 0.25) %	Cytotoxicity (MCF-7 cells): DTX PMs (IC_{50} = 67.84 ± 13.03 nM) > free DTX (IC_{50} = 119.51 ± 32.63 nM); The TIR in bearing MCF-7 cells: DTX PMs > DTX blank PMs.	2020[32]

(*Continued*)

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Table 2 (Continued).

Drug Delivery System	Ingredients	Characterization	Pharmacokinetics/TissueDistribution/Efficacy	Year, Refs.
DTX Polymer nanomicelles	LCA, PEG.	Size: ~ 160 nm PDI: 0.09	Tumor growth volume in bearing 4T1 nude mice↓; Pharmacokinetic: C_0↑; AUC↑; Cytotoxicity: LCA-DTX-PEG NMs > DTX.	2021[33]
DTX loaded β-CD	β-CD, PPG, EPI.	Mean Size: (223.36 ± 17.73) nm PDI: 0.13 ± 0.09 EE: (54.53 ± 2) %	MDA-MB-231 cells: cell uptake, cytotoxicity and apoptosis: DTX β-CD NPs > DTX; Pharmacokinetic: AUC↑, MRT↑; The tumor volume↓.	2021[34]
DTX loaded PAM-PBLG-b-TPGS Nanoparticles	PAM-PBLG-b-TPGS.	Mean Size: (205.8 ± 5.74) nm PDI: 0.187 ± 0.005 EE: (89.7 ± 0.7) % DL: (8.97 ± 0.3) %	Cell viability of Hela and MCF-7 cells: DTX-loaded PAM-PBLG-bTPGS < DTX-loaded PAM-PBLG; Cytotoxicity: DTX-loaded PAM-PBLG-bTPGS > DTX-loaded PAM-PBLG; Cellular uptake↑; The tumor volume↓.	2019[35]
DTX loaded mPEG-PLA Nanoparticles	mPEG-PLA.	Mean Size: 264.3 nm Zeta potential: (−33.79 ± 7.08) mV EE: 62.22% DL: 1.47%	Cytotoxicity: MCF-7 cells, DTX-mPEG-PLA-NPs: (IC_{50} = 2.02 ± 0.57 μg/mL) > DTX: (IC_{50} = 4.63 ± 1.64 μg/mL).	2023[36]
FPNs–DTX nanoparticles	PLGA, Chlorofor.	EE: (68.7 ± 4.2) % DL: (28.7 ± 1.8) %	DTX > 10nM: Cytotoxicity: FPN_3-DTX > $PLGA_3$-DTX>DTX; Cellular uptake: FPN_3-DTX < $PLGA_3$-DTX < DTX.	2020[37]
DTX loaded Tact-D-HC-P nanoparticles	TPGS, HPMC, Chitosan, PVA.	Mean Size: (180 ± 46.19) nm Zeta potential: (−35.9 ± 4.7) mV PDI: 0.312 ± 0.02	MDA-MB-231 cells: viabilities: Tact-D-HC-P < HTCD-P < HTCP-D < DTX.	2020[38]
Dextran-DHA-DTX conjugate	DHA, Dextran.	Mean Size: (98.0 ± 6.4) nm Zeta potential: (−24.1 ± 1.5) mV DL: (16.6 ± 1.4) %	MCF-7 cells: DTX: IC_{50} = 6.48 ± 2.61ng/mL, conjugate 22: IC_{50} = 9.48 ± 3.12 ng/mL; Pharmacokinetic: C_{max}↑; AUC↑.	2022[39]
Polymer-DTX complex	PMBA: 50 mg, DTX: 0.8 mg.	Mean Size: (27.0 ± 0.1) nm Zeta potential: (−11.8 ± 1.6) mV PDI: 0.24	Cytotoxicity in MCF-7 cells: PMBA-DTX > DTX > PMB-DTX.	2020[40]
LPHNPs-DTX	LPHNPs.	Mean Size: (143.47 ± 5.12) nm Zeta potential: (−12.22 ± 0.42) mV PDI: 0.26 ± 0.07 EE: (69.8 ± 2.83) % DL: (13.14 ± 0.37) %	Cytotoxicity: LPHNPs-DTX > DTX; The rate of cell viability↓; anti-tumor property↑; cellular uptake efficiency↑; Pharmacokinetics: MRT↑; $t_{1/2}$↑; AUC↑; The tumor volume↓.	2019[41]
DTX-loaded liposomes	HSPC, KW101, DSPE-PEG_{2000}.	Mean Size: 93 ~ 112 nm PDI: 0.028 ~ 0.098	Cytotoxicity: LDK > LD > DTX; Pharmacokinetic: AUC↑; $t_{1/2}$↑.	2021[42]
DTX-loaded liposomes	Coumarin-6, Cholesterol, DSPC, DSPE-$mPEG_{2000}$, TPGS.	Mean Size: (140.9 ± 6.0) nm Zeta potential: (0.196 ± 0.08) mV EE: (99.0 ± 0.9) % DL: (8.4 ± 0.01) %	Cytotoxicity: MCF-7 and MCF-7/ADR cells: TPGS-chol-liposome > PEG-chol-liposome > DSPC-chol-liposome > DTX; Cellular uptake↑; The percentage of apoptotic cells↑.	2019[43]
DTX loaded nanoliposomes	HSPC/$mPEG_{2000}$-DSPE /DPPG/Chol.	Mean Size: (116 ± 1.9) nm Zeta potential: (−13.8 ± 0.0) mV PDI: 0.11 ± 0.00 EE: (67.18 ± 6.6) %	In vitro cytotoxicity: MCF-7 cells: DTX loaded nanoliposomes (IC_{50} = 22.99 μg/mL) > Taxotere® (IC_{50} = 48.35 μg/mL); Tumor growth↓; The survival time↑.	2020[44]

(*Continued*)

Table 2 (Continued).

Drug Delivery System	Ingredients	Characterization	Pharmacokinetics/TissueDistribution/Efficacy	Year, Refs.
SLN-DTX	Comprito, Span 80, Pluronic F127.	Mean Size: (126 ± 5.0) nm Zeta potential: (−15 ± 0.5) mV PDI: 0.19 ± 0.01 EE: (86 ± 2.4) % DL: (2 ± 0.12) %	Cytotoxicity: MCF-7 cells: SLN-DTX (IC_{50} = 1.04 μg/mL) > free DTX (IC_{50} = 12.19 μg/mL).	2020[45]
DTX-SLNs	GMS, DSPE-PEG_{2000}.	Mean Size: 100 nm; PDI: 0.01 ~ 0.7; Zeta potential: −19 mV	Drug accumulation release percentages in 24 hours: 63%; Cytotoxicity: DTX-SLNs > DTX.	2021[46]
NLC-DTX	CO.	Mean Size: (221.5 ± 2.5) nm Zeta potential: (−36.0 ± 1.2) mV PDI: 0.18 ± 0.03 EE: ~ 100% DL: 1.5%	Drug accumulation release percentages in first 10 hours: 45%; The cell viability rate of 4T1 cells: DTX: 26.5 ± 1.3%, NLC_{DTX}: 14.0 ± 0.7%.	2022[47]
DTX loaded SF-nanoparticles	Silk-fibroin.	Mean Size: (198.1 ± 3.9) nm Zeta potential: (−26.6 ± 0.8) mV EE: (72.36 ± 1.6) % DL: (47.23 ± 2.5) %	MCF-7 cells: DTX-loaded SF-NPs: IC_{50} = 49.7 μg/mL; DTX: IC_{50} = 56.07 μg/mL; Cellular uptake: MCF-7 fluorescence signals↑; The rate of apoptosis↑.	2021[48]
DTX-sHDL nanoparticles	DMPC, DPPC, HSPC, POPC.	Mean Size: 20 nm Zeta potential: (−26.6 ± 0.8) mV EE: 66.5% DL: 2.01%	MCF-7 cells: DTX-sHDL: IC_{50} = 1.113 lg/mL; DTX: IC_{50} = 29.77 lg/mL; The average volume of tumors↓.	2019[49]
DTX HPVs	HPVs.	Mean Size: (124.2 ± 7.6) nm PDI: 0.21 ± 0.12 Zeta potential: (−35.2 ± 3.1) mV EE: (74.9 ± 1.4) % DL: (11.2 ± 1.3) %	MCF-7 cells: DTX HPVs: IC_{50} = 2.90 ± 0.58 μM, DTX: IC_{50} = 5.65 ± 0.95 μM; Apoptotic index: DTX HPVs > DTX liposome > DTX SCOPE dispersion > DTX; Pharmacokinetics: AUC↑; C_{max}↑; MRT↑; $t_{1/2}$↑.	2020[50]
DTX-span 20, DTX-span 80	Span 20®, Span 80®.	DTX-span 20 EE: 69.6% Zeta potential: −29 mV DTX-span 80: EE: 74.0%; Zeta potential: −27 mV	MDA-MB-231 cells: DXL-Span 20: IC_{50} = 4.7 nmol/L, DTX-Span 80: IC_{50} = 2.4 nmol/L, DTX: IC_{50} = 122.4 nmol/L; Pharmacokinetic: C_{max}↑; AUC↑.	2024[51]
CNTnol-APA-DTX	CNTnols, APA.	Mean Size: (86.31 ± 1.02) nm PDI: 0.113 Zeta potential: (−41.6 ± 0.17) mV DL: (51.62 ± 0.43) %	Pharmacokinetic: AUC↑; $t_{1/2}$↑; Cellular uptake (MDA MB-231 cells): CNTnol APA-DTX > DTX.	2019[52]

Abbreviations: DTX, docetaxel; LPHNPs, Lipid-polymer hybrid nanoparticles; SLNs, Solid lipid nanoparticles; NLCs, nanostructured lipid carriers; HPVs, Highly permeable vesicles; CNTs, Carbon Nanotubes; NPs, Nanoparticles; NMs, Nanomicelles; sHDL, synthesised high-density lipoprotein; PDI, polydispersity index; AUC, area under the curve; C_0, concentration; C_{max}, maximal concentration; EE, Encapsulation Efficiency; DL, Drug Loading; MRT, mean residence time; $t_{1/2}$, half-life; TIR, tumor inhibition rate; ↑, increase; ↓, decrease; >, greater than; <, less than.

Polymer Nanoparticles

Polymeric nanoparticles represent an innovative approach to drug delivery and have been widely used in cancer therapy.[54] Their nanoscale dimensions enhance targeted cellular uptake and efficient traversal of biological barriers. Utilizing a broad spectrum of polymerization and functionalization methods, these nanoparticles facilitate accurate drug delivery, bolster stability, and augment bioavailability, all while reducing adverse effects. Polymeric nanoparticles offer superior stability and versatility compared to conventional carriers.[55] Jain et al[34] used the formed crosslinked cyclodextrin nanoparticles (β-CD NPs) loaded with DTX to form DTX β-CD NPs. In vivo pharmacokinetics showed

that the mean residence time (MRT) and AUC of DTX β-CD NPs were about 5 times and 2 times higher than those of Docepar®, respectively, which prolonged the release ability of DTX. In vitro experiments demonstrated that the cellular uptake, cytotoxicity and apoptosis-inducing ability of DTX β-CD NPs were superior to that for free DTX. Antitumor activity studies demonstrated that tumor volume in the DTX β-CD NPs group was reduced by twofold compared to the Docepar® group, with no evidence of short-term nephrotoxicity. Wang et al[35] prepared a nanoparticle (DTX-PAM-PBLG-b-TPGS NPs) with a carrier of PAMAM poly (γ-L-glutamic acid benzyl ester)-b-D-α-tocopherol polyethylene glycol 1000 succinate (PAM-PBLG-b-TPGS) and loaded with DTX. Compared with free DTX, DTX-PAM-PBLG-b-TPGS NPs showed stronger cytotoxicity (lower survival) and higher uptake in MCF-7 cells, and also had strong anti-tumor effects. However, the study assessed safety solely by monitoring changes in mouse body weight and tumor tissue histopathology. No pharmacokinetic studies were conducted to elucidate the absorption, distribution, metabolism, and excretion patterns of the drug within the body, nor were long-term toxicity tests performed. Miraj et al[36] prepared DTX loaded methoxy polyethylene glycol-poly l-lactic acid (mPEG-PLA) nanoparticles (DTX-mPEG-PLA-NPs). Compared with free DTX, DTX-mPEG-PLA-NPs exhibited higher cytotoxicity to both MCF-7 and MDA-MB-231 BC cell lines. However, the study also has limitations, such as a relatively high PDI (0.524), a lack of long-term stability data, and the absence of animal studies to validate in vivo efficacy, safety, and pharmacokinetics. Lai et al[37] prepared DTX-coated fucoidan-PLGA nanoparticles (FPN-DTX), FPN-DTX showed highly uniform particle size, good colloidal stability and high drug encapsulation ability. Compared with PLGA-DTX and DTX, FPN-DTX exhibited better cytotoxicity and effectively exerted anti-cancer ability against MDA-MB-231 cells. Tran et al[38] successfully prepared three polymeric composite structures composed of hydroxypropyl methylcellulose (HPMC), chitosan (CS), polyvinyl alcohol (PVA), and D-α-tocopherol polyethylene glycol succinate (TPGS), successfully prepared three DTX-loaded nanoparticles: HTCD-P, HTCP-D, and Tact-D-HC-P. In their effects on MDA-MB-231 cells, all drug-loaded nanoparticles exhibited significantly greater cytotoxicity than free DTX, with this difference becoming more pronounced with extended incubation times. After incubation at a concentration of 75 μM for 48 hours, the cell survival rates in the Tact-D-HC-P, HTCD-P, and HTCP-D nanoparticle groups were 1.18%, 6.33%, and 22.79% respectively, significantly lower than that in the free DTX group (41.70%). This outcome aligns with the cellular toxicity pattern, further confirming that drug-loaded nanoparticles more effectively suppress cancer cell activity than free DTX. Dong et al[39] covalently coupled DTX and docosahexaenoic acid (DHA) with dextran to form a dextran-DHA-DTX coupling. The maximal concentration (C_{max}) and AUC of the coupling were significantly increased compared to free DTX, suggesting a higher concentration of the drug in vivo and a longer cycle time of the coupling. The conjugate effectively eradicated tumors in a nude mouse model with MCF-7cells, achieving this without inducing any noticeable systemic side effects. Otaka et al[40] utilized a novel phospholipid polymer (PMBA) to prepare the PMBA-DTX complex, which exhibited a mean particle size of 27.0 ± 0.1 nm. The PMBA-DTX complex exhibited better anti-tumor effects than free DTX on MDA-MB-231, MCF-7 and 4T1 BC cell lines. However, the in vivo release behaviour of DTX remains uncharacterised. In vivo studies lack safety assessments, pharmacokinetic data, and long-term toxicity evaluations.

Lipid Polymer Nanoparticles

Lipid-polymer hybrid nanoparticles (LPHNPs) represent a cutting-edge drug delivery platform that capitalizes on the strengths of both liposomes and polymer nanoparticles, while mitigating their respective drawbacks.[56] LPHNPs offer several unique advantages compared to other types of nanocarriers, including the lipids, biocompatible polymers, and polymer-lipid combinations used to prepare them, as well as their excellent ability to co-encapsulate different therapeutic and imaging reagents.[57] Jadon et al[41] prepared DTX lipid polymer hybrid nanoparticles (LPHNPs-DTX). The LPHNPs-DTX formulation showed greater cytotoxic effects and greater cellular uptake compared to free DTX. The total number of MDA-MB-231 cells damaged (87%) was higher with LPHNPs-DTX treatment compared to free DTX (51%). However, further in vivo biodistribution and antitumor efficacy studies are required to validate the in vitro findings. Although LPHNPs combine the biocompatibility of liposomes with the structural stability of polymeric nanoparticles, their practical application still reveals issues such as complex processing, poor reproducibility, and insufficient long-term stability.

Liposomes

Liposomes are colloidal particles, these spherical bilayer vesicles contain cholesterol and phospholipids, which usually arise spontaneously as the lipids disperse into the aqueous phase. In addition, they have various advantages such as biodegradability, good biocompatibility, non-toxicity, doping with hydrophobic and hydrophilic substances, and high bioavailability.[58] Zawilska et al[42] prepared DTX liposomes containing hydrogenated soybean phosphatidylcholine (HSPC), 3-n-pentadecylphenol (KW101) and DSPE-PEG_{2000}. DTX-containing liposomes showed higher cytotoxicity to MCF-7 cells compared to free DTX. The AUC, half-life ($t_{1/2}$), and MRT of DTX-containing liposomes were significantly higher than those of the control group, with longer circulation time and improved bioavailability. However, this study has not yet established a mouse tumor model and lacks key efficacy indicators, such as tumor inhibition rate and survival time. Li et al[43] prepared vitamin E D-alpha-tocopherol polyethylene glycol 1000 succinate (TPGS) encapsulated DTX liposomes. Their liposomes had a particle size of 140.9 ± 6.0 nm. The IC_{50} of TPGS-chol-liposomes in MCF-7 and MCF-7/ADR cells was 1.99 and 1.91 times lower than that of free DTX, respectively, suggesting that TPGS-chol-liposomes have higher cytotoxicity to MCF-7 and MCF-7/ADR cells, and also significantly increased apoptosis (55.9% and 32.6%). The in vitro efficacy advantages are clearly demonstrated, yet lack validation through animal models. The in vitro cellular environment differs significantly from the in vivo tumor microenvironment, precluding determination of the liposome's in vivo targeting capability. Roghayyeh et al[44] prepared DTX loaded by hydrogenated soybean phosphatidylcholine (HSPC), polyethylene glycol-modified DSPE ($mPEG_{2000}$-DSPE), cholesterol (Chol), and different phosphatidic acids (such as DPPG, DSPG) (HSPC/$mPEG_{2000}$-DSPE/DSPG/Chol) nanoliposomes. DTX-liposomes exhibited higher cytotoxicity to MCF-7 cells than free DTX. Moreover, DTX-liposomes significantly retarded tumor growth (TIR: 72.83%) and prolonged survival time in BC tumors. Although this DTX liposome carrier demonstrates advantages in terms of biocompatibility and passive targeting, the residual organic solvents and stability during its preparation process are difficult to control.

Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

SLNs are aqueous dispersions in which the colloidal particles consist of biodegradable solid lipids. SLNs have several advantages over other drug carriers due to their physical stability, protection of the encapsulated drug from decomposition, provision of controlled drug release, and excellent acceptability.[59] SLNs are attractive nano-drug delivery systems (NDDS) with high structural stability and biocompatibility and is considered a less toxic alternative to polymer-based nanoparticles.[60] Márcia et al[45] successfully prepared SLN-DTX using Compritol 888 ATO as lipid matrix and Pluronic F127 and Span 80 as surfactants. In vitro experiments showed that SLN-DTX displayed higher cytotoxicity and higher cellular uptake in MCF 7 cells compared to free DTX. SLN-DTX significantly inhibited tumor growth (TIR: 92.7%) without significant systemic toxicity. Nadia et al[46] successfully prepared DTX-SLNs with good particle size uniformity stability (100 nm), low PDI (0.2) and excellent encapsulation rate. DTX-SLNs showed good performance in terms of solubilisation and drug release from the system. DTX-SLNs showed high cytotoxicity against HCC 1954 BC cells. However, the study exhibits significant limitations: in vivo experiments are entirely absent, with no tumor-bearing animal models established to validate tumor accumulation, therapeutic efficacy, or adverse effects.

Nanostructured lipid carriers (NLCs) are formed by replacing some of the solid lipids with liquid lipids to form a drug-encapsulated skeleton.[61] NLCs are increasingly utilized in the field of drug delivery due to their superior ability to encapsulate hydrophobic drugs, their outstanding biocompatibility, and their amenability to surface modification. These features enhance the targeting of chemotherapeutic agents and extend their circulation time within the body.[62] SLNs are structurally simple, low-toxicity lipid nanoparticles suitable for basic drug delivery; NLCs significantly enhance drug loading capacity, stability, and controlled release through the incorporation of liquid lipids, making them particularly well-suited for complex requirements such as high drug loading, controlled release, and targeted delivery. Carvalho et al[47] prepared an NLC formulation using copaiba oil (CO) as an excipient for loading DTX (NLC_{DTX}). It was demonstrated that the formulation exhibited excellent stability, effectively promoting sustained and stable DTX release, prolonging drug action and improving bioavailability. NLC_{DTX} showed good cytotoxicity against both 4T1 and MCF-7 cells, with greater inhibition of cell viability than commercial DTX. However, this study also exhibits significant limitations: it failed to simulate the impact of the tumor's acidic

microenvironment on drug release; it entirely lacked in vivo experiments, with no tumor animal models established to validate tumor targeting, in vivo efficacy, or adverse reactions.

Protein Nanoparticles

Protein nanoparticles are formed by arranging several natural or modified proteins into nano-sized assemblies.[63] Leveraging their biodegradability, bioavailability, and cost-effectiveness, these nanoparticles are gaining widespread application across diverse settings. They are increasingly substituting for numerous materials that lack biocompatibility and pose detrimental effects on the environment.[64] Saqr et al[48] prepared DTX-loaded filipin protein nanoparticles (SF-NPs). In vitro cellular studies demonstrated that DTX in SF-NPs significantly improved the killing ability of BC cells and enhanced the uptake of DTX by BC cells compared with free drug. SF-NPs loaded with DTX had a strong cytotoxic effect on MCF-7 cells (IC_{50} = 49.76 μg/mL) compared to free DTX (IC_{50} = 56.07 μg/mL). However, the system exhibits significant shortcomings, with a complete absence of in vivo experiments. Pharmacokinetics, tumor targeting efficacy, and long-term toxicity remain unknown. Gong et al[49] synthesised high-density lipoprotein (sHDL) based nanocarriers loaded with atorvastatin (ApoA-I) mimetic peptide and DTX (DTX-sHDL). The nanoparticles formulated with DTX and sHDL have shown to boost the internalization of DTX into cells, intensify its toxic effects on MCF-7 cells, and reduce unintended harmful impacts on healthy cells. DTX-sHDL nanoparticles inhibited tumor growth (TIR: 74.90%) better than the free DTX group.

Highly Permeable Vesicles (HPVs)

HPVs are nano-sized vesicles with the dual advantage of a nanocarrier and a mixture of synergistic penetration enhancers. HPVs are composed of a synergistic combination of phospholipids and penetration enhancers (SCOPE). HPVs have a good biocompatibility, drug-carrying capacity for both hydrophilic and hydrophobic drugs, and dermal penetration.[65] Minal et al[50] prepared DTX-HPVs using HPVs as an effective nanocarrier. DTX-HPVs exhibited homogeneous deformable vesicles, which significantly improved skin permeation profiles, with a sustained release of the drug. DTX-HPVs showed improved cellular uptake, increased cytotoxicity and apoptotic index in MCF-7 and MDA-MB-231 cells. HPVs exhibit slow skin metabolism of phospholipids, with prolonged use leading to accumulation in the epidermis and disruption of lipid metabolism. Their structural stability is poor, making them prone to drug leakage and skin irritation caused by permeation enhancers. They also present challenges in terms of poor tolerability and difficulties in industrialisation. Ajdari et al[51] prepared DTX loaded nanovesicles (DTX-Span 20, DTX-Span 80) using two nonionic surfactants Span 20 and Span 80. The EE of DTX was 69.6% and 74.0% for DTX-Span 20 and DTX-Span 80, respectively, indicating that the prepared nanovesicles could encapsulate DTX more efficiently. The plasma concentration of DTX-Span 80 in rats was higher than that of DXL-Span 20, suggesting it has better bioavailability. Compared with free DTX, both DTX-Span 20 and DTX-Span 80 showed higher cytotoxicity against MDA-MB-231 cells, and the cytotoxic effect of DXL-Span 80 was better than that of DTX-Span 20.

Carbon Nanotubes (CNTs)

CNTs possess distinctive physical and chemical properties, such as a high aspect ratio and a large surface area, abundant surface chemical functionality, and nanoscale stability, and carbon nanotubes and their derived materials have a wide range of applications in various in the industrial and medical fields, as well as a great potential in drug delivery.[66] Thotakura et al[52] coupled DTX with aspartic acid (APA)-labelled carbon nanotubes (CNTnols) to form a CNTnol-APA-DTX conjugate. Compared with pure DTX (IC_{50} = 36.98 nM), CNTnol-APA-DTX conjugate (IC_{50} = 10.89 nM) resulted in decreased proliferative capacity of cells and enhanced MDA-MB-231 cell cytotoxicity. The bioavailability of the drug was almost 1.7-fold higher and the half-life was 1.4-fold longer, ensuring that the drug stays longer and increases the anti-tumor effect. However, in vivo studies have only conducted pharmacokinetic experiments, with no tumor models yet established to evaluate antitumor efficacy. CNTs exhibit an extremely low degradation rate, rendering them difficult for the body to clear effectively. Their preparation process is complex and prone to agglomeration, making it challenging to form stable dispersions in aqueous solutions. This not only diminishes their application performance but also accelerates systemic clearance by the body.

Active Targeted Drug Delivery System

Active targeting, also known as ligand-mediated targeting, is accomplished by conjugating a specific ligand or antibody to a nanocarrier. This strategy is fundamentally based on the recognition between paired ligands and receptors or between antigens and antibodies on the surface of tumor cells.[67] It can enhance the tumor uptake of the drug delivery system and boost the efficacy of anticancer drugs. What's more, since the reagent system is designed to specifically bind to receptors that are overexpressed on tumors but not expressed by normal cells, it can also significantly reduce adverse side effects. These actively targeted delivery systems exhibit better performance, such as increased cytotoxicity to tumor cells as well as reduced side effects, compared to untargeted delivery systems.[68] Surface receptors that have been used for targeting in BC cells include: FR, Human epidermal growth factor receptor 2 (HER-2), $\alpha_v\beta_3$, G protein-coupled estrogen receptor (GPER), siglec-1 receptor, epithelial cell adhesion molecule receptor (EpCAM), neurofibrillary protein receptor 1 (NRP-1), and cluster of determination 44 receptor (CD44). These receptors are usually overexpressed on breast cancer cells and less or not expressed on normal cells, making them ideal targets for targeting. The related key points have been summarized in Table 3.

G Protein-Coupled Estrogen Receptor (GPER)

GPER is a member of the extensive family of G protein-coupled receptors (GPCRs), characterized by the presence of seven transmembrane helices within the cytoplasmic membrane. GPER is highly expressed in estrogen receptor-positive BC cell lines such as MCF-7, T-47 D, and MDA-MB-361. Its high level of activity and over-expression in BC is associated with the progression of the tumor, its metastasis, and a reduction in survival rates.[87–89] Raloxifene (RA), a selective estrogen receptor modulator (SERM), binds to GPER and exerts a stimulatory effect on breast cancer cells. Varshosaz et al[69] prepared DTX-loaded RA-targeted polymer micelles consisting of poly (styrene-maleic acid)-poly

Table 3 Actively Targeted Drug Delivery Systems for DTX

Drug Delivery System	Ligand/ Antibody	Receptor/ Antigen	Characterization	Pharmacokinetics/Tissue Distribution/ Efficacy	Year, Refs.
DTX-loaded SMA-PAEEI-PEG-RA	RA	GPER	Mean Size: (128.5 ± 4.7) nm PDI: 0.4 ± 0.0 Zeta potential: −10.5 mV EE: 60.3 ± 2.0%	TIR: DTX-loaded SMA-PAEEI-PEG-RA micelles (TIR: 78.57%) > DTX-loaded SMA-PAEEI-PEG micelles > free DTX.	2019[69]
DTX-SAPL liposomes	SA	Siglec-1	Mean Size: (96.2 ± 4.05) nm PDI: 0.19 ± 0.02 Zeta potential: (−27.4 ± 1.28) mV EE: 98.1 ± 0.27%	Drug accumulation release percentages after 24 hours: 96.41 ± 4.2%; Cytotoxicity: DTX-SAPL > DTX-CL > DTX-PL > DTX-S; The tumor weight: DTX-SAPL < DTX-CL < DTX-S.	2023[70]
DTX-PEG-EpCAM-MNs	EpCAM	EpCAM	Mean Size: (167.0 ± 1.28) nm PDI: 0.124 Zeta potential: 28.7 mV EE: 82.43% DL: 7.16%	Cytotoxicity: cell survival rate↓; Trapping efficiency: DTX-PEG-EpCAM-MNs > DTX-PEG-MNs; The number of isolated tumor cells↑.	2020[71]
FA-PEG-DTX	Folic acid	Folate	Mean Size: (181 ± 10.1) nm PDI: 0.23 Zeta potential: −9.4 mV EE: 82 ± 9.5%	Cytotoxicity: FA-PEG-DTX > PEG-DTX; Tumor growth inhibitory effects: FA-PEG-DTX > PEG-DTX; In vitro: 4T1 cellular uptake↑.	2021[72]
DTX-Loaded FA-PEG-HEP-CA-TOC Polymeric Micelles	Folic acid	Folate	Mean Size: (88.80 ± 7.27) nm PDI: 0.07 ± 0.014 Zeta potential: (−17.44 ± 4.22) mV EE: (85.07 ± 3.33) % DL: 4.41 ± 0.17%	In Vitro: cellular Uptake (4T1): DTX/FA-PEG-HEP-CA-TOC > DTX/HEP-CA-TOC; Cytotoxicity: DTX/FA-PEG-HEP-CA-TOC > DTX/HEP-CA-TOC > DTX/Tween®80 > DTX.	2020[73]

(*Continued*)

Table 3 (Continued).

Drug Delivery System	Ligand/ Antibody	Receptor/ Antigen	Characterization	Pharmacokinetics/Tissue Distribution/ Efficacy	Year, Refs.
F-DTX-LPNs	Folic acid	Folate	Mean Size: 115.17 nm PDI: 0.205 Zeta potential: −9.13 mV EE: 80.14%	In vitro: MDA-MB231 cellular uptake: F-DTX-LPNs > DTX-LPNs; Invitro: Cytotoxicity: F-DTX-LPNs > DTX-LPN > DTX; Apoptosis: F-DTX-LPNs > DTX-LPNs > DTX; Pharmacokinetics: C_{max}↑; AUC↑; $t_{1/2}$↑.	2020[74]
FA/PBAE/DTX-NPs	Folic acid	Folate	Mean Size: (104 ± 6) nm PDI: 0.23 ± 0.03 Zeta potential: (5.5 ± 3.2) mV EE: 78.6 ± 2.3% DL: 6.8 ± 0.7%	Cytotoxicity and apoptosis (4T1 cells): FA/PBAE/DTX-NPs > PBAE/DTX-NPs > DTX; Highly distributed in the liver and spleen; The TIR: FA/PBAE/DTX-NPs > PBAE/DTX-NPs > DTX.	2021[75]
FA-PEG-DA-PAE-Chol nanoparticles/ DTX	Folic acid	Folate	Mean Size: (182.38 ± 1.57) nm PDI: 0.134 ± 0.03 Zeta potential: (−1.18 ± 0.01) mV EE: 55.72 ± 1.76% DL: 5.53 ± 0.30%	Cytotoxicity (MCF-7 cells): FPDPCNPs/DTX > PEGPAE/DTX > PDPCNPs/DTX; Cellular uptake and apoptosis (MCF-7 cells): FPDPCNPs/DTX > PDPCNPs.	2023[76]
Apt-DTX-NPs	DNA	HER-2	-	Cytotoxicity: Apt-DTX-NPs > DTX-NPs>DTX; Drug accumulation release percentages: 47.69 ± 1.64%.	2019[77]
DTX-daPCL/iNGRt-Palm NPs	iNGRt	NRP-1	Mean Size: (96 ± 8) nm PDI:0.2 Zeta potential: (+33 ± 2) mV EE: 96 ± 3% DL: 4.26%	Cytotoxicity: DTX-daPCL/iNGRt-Palm NPs > DTX-daPCL NPs > DTX; In reducing the tumor volume: DTX-daPCL /iNGRt-Palm > DTX-daPCL NPs > DTX > empty NPs.	2023[78]
DTX-H40-PEG-cRGDfc	cRGDfc	$\alpha_v\beta_3$	Mean Size: (117 ± 3.19) nm EE: 99.66 ± 4.35%	MDA-MB-231 and 4T1 cells: cytotoxicity: DTX-H40-PEG-cRGDfc > DTX-H40-PEG-OCH3 > DTX.	2024[79]
DTX loaded RGD-PLGA-NPs	RGD	$\alpha_v\beta_3$	EE: 18.2 ± 5%	4T1 cells viability: DTX-RGD-PLGA > DTX-Ctrl-PLGA > DTX; In Vivo: anti-cancer: RGD-PLGA>Ctrl-PLGA>DTX.	2022[80]
DTX-X-PHS@NPs	HA	CD44	Mean Size: 132 nm	Cytotoxicity: DTX-X-PHS@NPs > DTX; TIR: DTX-XPHS@NPs > X-PHS@NPs > DTX.	2019[81]
DTX-CMHN	HA	CD44	Mean Size: 77 nm PDI: 0.11 DL: 76.3–80.4%	In Vitro: 4T1-Luc breast cancer cells: DTX-CMHN: IC_{50} = 0.91 μg/mL, DTX: IC_{50} = 1.27 μg/mL; Pharmacokinetics: AUC↑; $t_{1/2}$↑; Drug accumulation: DTX-CMHN > DTX-MHN > DTX.	2019[82]
CDPM/D nanoparticles	CSA	CD44	Mean Size: (286.7 ± 6.0) nm PDI: 0.18 ± 0.03 Zeta potential: (−15.69 ± 0.49) mV EE: 76.03 ± 0.86%	Cytotoxicity: CDPM/D NPs > CDP/D NPs > DTX; Pharmacokinetics: AUC↑; $t_{1/2}$↑; MRT↑; Growth suppression and the penetration efficiencies: CDPM/D NPs > CDP/D NPs > DTX.	2020[83]

(*Continued*)

Table 3 (Continued).

Drug Delivery System	Ligand/ Antibody	Receptor/ Antigen	Characterization	Pharmacokinetics/Tissue Distribution/ Efficacy	Year, Refs.
HA-DTX-Dendron	HA	CD44	Mean Size:(122 ± 4) nm PDI: 0.174 Zeta potential: (−29 ± 2) mV	Cellular uptake of MCF-7 cells↑; TIR: HADD: 99.71%, DTX: 93.22%.	2021[84]
DTX-LF-CST nanoconjug-ate	LF	TfR	Mean Size: (157.8 ± 4.6) nm Zeta potential: (+19.0 ± 0.35) mV	Cytotoxicity and cellular uptake (MCF-7 cells): DTX-LF-CST > DTX; Tumor growth inhibition: DTX-LF-CST > DTX +CST > DTX > CST.	2021[85]
Rg3-Lp/DTX	Rg3	Glut1	Mean Size: (80.3 ± 3.7) nm EE: 91.0 ± 2.6% DL: 6.5 ± 0.2%	Early apoptotic 4T1 cells: Rg3-Lp/DTX > C-Lp/ DTX > Nanoxel-PM > DTX; Cytotoxicity: Rg3-lp/DTX > Rg3/DTX > DTX.	2022[86]

Abbreviations: PDI, polydispersity index; EE, Encapsulation Efficiency; DL, Drug Loading; AUC, area under the curve; C_{max}, maximal concentration; $t_{1/2}$, half-life; TIR, tumor inhibition rate; -, no data. ↑, increase; ↓, decrease; >, greater than.

(amide-ether-ester-imide)-poly (ethylene glycol) (SMA-PAEE-PEG). DTX-loaded SMA-PAEEI-PEG-RA micelles (TIR: 78.57%) showed stronger inhibition of tumor growth in mice with BC loaded hormonal tumors compared to non-targeted micelles (TIR: 57.14%) and free DTX (TIR: 51.19%) and increased the survival rate of mice with targeted micelles. DTX-loaded RA-targeted micelles showed higher drug concentrations in tumor tissues than free DTX, suggesting that targeted micelles may be taken up by tumor cells via endocytosis of GPER receptors. However, the model is restricted to murine tumors and does not provide pharmacokinetic or release behaviour data. The preparation process is complex and stability studies are incomplete. These shortcomings significantly limit its practical potential for translating from laboratory research to clinical application.

Siglec-1 Receptor

The receptor siglec-1, also known as salivary acid adhesin or CD169, is specifically expressed at high levels on the surface of TAMs. Siglec-1 readily binds to salivary acid (SA), which serves as its specific ligand. Given its restricted and predominantly TME-associated expression, siglec-1 emerges as a promising target for drug delivery systems modified with SA, aiming to target TAMs in cancer therapy.[90–92] Tran et al[70] synthesised a salivary acid-polyethylene glycol coupling (DSPE-PEG_{2000}-SA) and modified it on drug-carrying liposomes to prepare three DTX-loaded liposomes, including conventional liposomes (DTX-CL), DSPE-PEG_{2000}-modified liposomes (DTX-PL) and SA-modified liposomes (DTX-SAPL). Surface-modified liposomes of SA enhanced cellular internalisation via SA-SA receptor interactions, with DTX-SAPL showing the highest cellular uptake. DTX-SAPL (IC_{50} = 4.89 μg/mL) showed higher cytotoxicity against 4T1 BC cells compared to non-targeted liposomes (DTX-PL and DTX-CL). The tumor weight of Balb/c mice bearing 4T1 xenografts in the DTX-SAPL group was significantly lower (314.1 ± 17.12 mg), which effectively inhibited the growth of tumor. DTX-SAPL-mediated cancer suppression may be achieved through active targeting of TAMs, which are highly concentrated at the tumor periphery, followed by gradual infiltration towards the tumor centre, ultimately resulting in extensive necrosis within the tumor core.

Epithelial Cell Adhesion Molecule (EpCAM) Receptor

EpCAM is extensively present on the surface of epithelial tissues. In BC, EpCAM is frequently employed as a marker for detecting tumor cells, as well as a surface marker for tumor-associated antigens and BC stem cells.[93] By modifying EpCAM-targeting ligands on the surface of drug carriers, the targeting of drugs to tumor cells can be improved, thereby enhancing therapeutic efficacy and reducing damage to normal cells. Song et al[71] modified MNs by combining PEG and EpCAM to construct long-circulating targeted drug-carrying microspheres (DTX-PEG-EpCAM-MNs) loaded with DTX. Owing to the targeting effect of EpCAM, DOX-PEG-EpCAM-MNs effectively recognise SK-BR-3 cells and exhibit stronger tumor cell inhibition, whereas DOX-PEG-MNs demonstrate the weakest inhibitory effect. EpCAM is also lowly

expressed in certain normal epithelial tissues, rendering its targeting specificity non-absolute and potentially inducing uptake in non-tumor tissues. Furthermore, this study suffers from the absence of long-term toxicity data and the complexity of industrialisation processes.

Folate Receptor (FR)

FR is a high-affinity membrane glycoprotein that is commonly overexpressed in a variety of tumor tissues including breast, brain, cervix, lung, colon, kidney and ovary. Folic acid (FA), as a small-molecule vitamin, has an extremely high affinity for the folate receptor and is able to bind specifically to the receptor. Therefore, FA is widely used as a ligand for active targeting, and by combining folic acid with drugs, nanoparticles or other drug delivery systems, targeted delivery of drugs can be achieved, thus increasing the concentration of drugs in tumor cells and enhancing therapeutic effects.[94,95] Faezeh et al[72] synthesised targeted micellar preparations (FA-PEG-DTX) using DTX, FA and PEG couplings as building blocks. FA-PEG-DTX exhibited higher cytotoxicity, drug uptake capacity and stronger tumor growth inhibition in 4T1 cells (folate receptor overexpression) compared to the PEG-DTX. Kazemi et al[73] synthesised folic acid-polyethylene glycol-heparin-Cis-Aconitic (CA) anhydride-alpha-Tocopherol (TOC) (FA-PEG-HEP-CA-TOC) conjugates and prepared DTX-loaded micelles (DTX/FA-PEG-HEP-CA-TOC). DTX/FA-PEG-HEP-CA-TOC showed higher cellular uptake and cytotoxicity in MCF-7 and 4T1 cells, and was more effective in inhibiting tumor growth (TIR: 87.86%) compared to DTX and non-targeted micelles. Sharma et al[74] prepared DTX-loaded folate-conjugated lipopolymer nanoparticles (F-DTX-LPNs). F-DTX-LPNs showed higher intracellular uptake, cytotoxicity and apoptosis-inducing potential and inhibited tumor cell proliferation compared to free DTX and non-targeted nanoparticles. F-DTX-LPNs demonstrate innovation in DTX targeted delivery, effectively enhancing the drug's water solubility, targeting efficiency, and safety profile. However, the study remains in the foundational exploratory phase, constrained by its failure to simulate the tumor microenvironment for drug release assessment. Zhang et al[75] prepared a novel type of pH-responsive lipid-polymer hybrid nanoparticles (FA/PBAE/DTX-NPs) consisting of a hybrid lipid shell and poly (β-amino ester) (PBAE) polymer core. The intracellular uptake efficiency of FA/PBAE/DTX-NPs was significantly improved through FA receptor-mediated endocytosis. Compared with free DTX and PBAE/DTX-NPs, FA/PBAE/DTX-NPs exhibited enhanced cytotoxicity, apoptosis-inducing ability and significant anti-tumor effect (TIR: 85.5%) and minimal systemic toxicity against 4T1 cells. Sui et al[76] prepared a novel nanoparticle (FPDPCNPs/DTX). FPDPCNPs/DTX showed higher cellular uptake and cytotoxicity than other nanoparticles in MCF-7 cells under a slightly acidic environment and FR-mediated targeting, and was most cytotoxic under acidic conditions (pH 5.5), with a significant antitumor effect on 4T1 cells (TIR: 81.99%). However, its encapsulation rate and drug loading capacity remain low (merely 5.53%), and liver accumulation indicates persistent risks of clearance via the reticuloendothelial system (RES). Furthermore, the FA ligand exhibits expression in normal tissues, leaving potential off-target toxicity inadequately addressed. Relying solely on a single animal model and lacking long-term toxicity assessments.

Human Epidermal Growth Factor Receptor 2 (HER-2) Receptor

HER-2 receptor is a transmembrane epithelial growth factor receptor that is amplified in 20–25% of human BC cases.[96] Aptamers are a class of short-stranded DNA or RNA molecules that fold into a specific three-dimensional structure according to a specific sequence, and they are able to bind to a specific target, displaying high affinity and specificity for binding to a defined target, a more stable alternative to antibodies, and easy to manufacture and modify.[97] HER-2 aptamer is a DNA or RNA oligonucleotide that specifically binds to the HER-2 receptor through its unique three-dimensional structure with high affinity and specificity for targeted delivery of drugs or diagnostic molecules to HER-2 over-expressing cancer cells. Ghassami et al[77] prepared novel HER-2-targeted Ecoflex® nanoparticles (Apt-DTX-NPs). Compared with free DTX, Apt-DTX-NPs showed higher cytotoxicity in both cell lines (BT-474 and MDA-MB-468) and were higher in HER-2 positive cell lines. The cellular uptake of Apt-DTX-NPs was significantly increased and was higher in HER-2 positive cell lines. In Apt-DTX-NPs-treated cells, the proportion of early apoptotic cells was significantly increased and the proportion of necrotic cells was decreased. Apt-DTX-NPs demonstrate innovative potential in targeted delivery for HER-2 positive breast cancer, effectively enhancing DTX's targeting capacity and in vitro efficacy while promoting cancer cell apoptosis. However, research remains confined to in vitro exploration

without validation in animal models. Consequently, its in vivo targeting capability and safety cannot be confirmed, nor have pharmacokinetic parameters or long-term toxicity been assessed.

Neuropilin-1 (NRP-1) Receptor

NRP-1 receptor is a non-tyrosine kinase transmembrane receptor. NGR peptide is a small molecule peptide capable of specifically binding to NRP-1 receptor overexpressed on tumor cells, and therefore can be used to target tumor cells.[98] Conte et al[78] prepared poly (ε-caprolactone) (daPCL) nanoparticles (DTX-daPCL/iNGRt-Palm NPs) functionalized with palmitoylated NGR peptide (iNGRt-Palm) loaded with DTX. DTX-daPCL/iNGRt-Palm NPs showed higher cytotoxicity in MDA-MB-231 cells, compared to unmodified nanoparticles (DTX-daPCL NPs). Due to the overexpression of NRP-1 receptor, NPs cellular uptake was efficiently driven to breast cancer cells with a significant increase in cellular uptake efficiency. DTX-daPCL/iNGRt-Palm NPs showed significant anti-tumor effects and more effective reduction of tumor volume. However, the present study currently lacks pharmacokinetic data, and the expression of NRP-1 in tumor tissue from different TNBC patients exhibits significant heterogeneity, which may lead to individual variations in targeting efficacy.

Integrin Protein Receptor ($\alpha_v\beta_3$)

$\alpha_v\beta_3$ integrins are heterodimeric cell surface molecules that are overexpressed in BC cells, making them an important target for chemotherapy.[99] Integrins are a class of heterodimeric transmembrane receptors that bind ligand fragments in the extracellular matrix (ECM), initiating signalling events that have a wide range of effects on cell survival, proliferation and migration.[100] Since $\alpha_v\beta_3$ integrins are also overexpressed on angiogenesis-associated endothelial cells, RGD peptides capable of binding specifically to $\alpha_v\beta_3$ integrins could be used for targeted therapies to enhance drug accumulation and efficacy in tumor tissues.[101] Korake et al[79] prepared targeted dendrimers loaded with DTX (DTX-H40-PEG-cRGDfc) using Boltron® H40 dendrimer macromolecule with PEG and cRGDfc peptide ligand (H40-PEG-cRGDfc) as a carrier. Since cRGDfc is present on the surface of NPs, it promotes the uptake of targeted NPs by breast cancer cells by binding to the $\alpha_v\beta_3$ integrin receptor,[102] and H40-PEG-cRGDfc showed higher uptake in MDA-MB-231 and 4T1 BC cells. DTX-H40-PEG-cRGDfc showed significant cytotoxicity compared to DTX and DTX-H40-PEG-OCH3. Di et al[80] prepared RGD-functionalized poly(lactic acid)-hydroxyacetic acid copolymer nanoparticles (RGD_PLGA-NPs) for loading DTX. in which RGD peptide-functionalized PLGAs. RGD peptide functionalized PLGA, which can have better anti-tumor efficacy by actively targeting $\alpha_v\beta_3$ integrins overexpressed in BC cells. RGD_PLGA-NPs showed higher intracellular uptake and significant anti-tumor effects compared to free DTX and non-targeted agents (PLGA-NPs). However, limitations exist: the study did not simulate the tumor's acidic microenvironment to investigate drug release, nor did it measure key pharmacokinetic parameters such as blood half-life, clearance rate, and tissue distribution. Consequently, it remains unclear whether the formulation enhances tumor targeting efficiency by prolonging circulation time.

Cluster of Differentiation 44 (CD44) Receptor

CD44 is a common marker of BC cancer stem cells, which functions as a co-receptor for a variety of extracellular matrix ligands. Hyaluronic acid (HA) is a very attractive ligand and CD44 can be specifically recognised by HA, suggesting that CD44 overexpressed on the surface of tumor cells can act as a specific receptor for targeted drug delivery.[103] Li et al[81] prepared DTX-loaded CD44-targeting PLGA nanoparticles (DTX-X-PHS@NPs) that could be coated off by using the photo-click crosslinking surfactant HA-g-Tet (X-PHS@NPs). Compared with free DTX, X-PHS@NPs were able to be effectively taken up by MCF-7 cells, showed good anti-tumor effect (TIR: 74%), and had good biocompatibility and safety. Fang et al[82] prepared multifunctional HA nanoparticles (DTX-CMHN) loaded with DTX. DTX-CMHN showed better anti-tumor, anti-migration and anti-invasive activities in CD44 overexpressing 4T1-Luc BC cells. DTX-CMHN significantly inhibited the growth and lung metastasis of primary 4T1-Luc tumors with lower toxicity than free DTX. Wang et al[84] prepared a stimuli-responsive dendritic HA-DTX coupling (HADD). HADD significantly increased the uptake efficiency of MDA-MB-231 cells by targeting the CD44 receptor via HA and also showed good anti-tumor effects (TIR: 99.71%). In addition, HADD significantly reduced the side effects of free DTX. Chondroitin sulphate (CS) is another ligand targeting the CD44 receptor. Its chemical structure resembles that of HA, offering numerous advantages including low immunogenicity and high biodegradability. The presence of multiple active functional groups such as

carboxyl and hydroxyl groups along its molecular chain enables modification with small-molecule drugs, rendering it suitable for cancer therapy.[104] Furthermore, reduction-responsive chondroitin sulphate A (CSA) has been effectively employed as an active targeting moiety, particularly for tumors overexpressing the CD44 receptor, significantly enhancing therapeutic delivery precision.[105] Lee et al[83] designed a new chondroitin sulfate (CSA)-deoxycholic acid (DOCA)-PEG-maleimide (MAL) (CDPM) nanostructures (CDPM/D NPs) loaded with DTX for targeting CD44 overexpressing MCF-7 BC cells. CDPM/D NPs showed higher cellular uptake efficiency, higher anti-proliferative effect and higher anti-tumor activity against MCF-7 cells compared to free DTX, and also exhibited longer blood circulation time and higher tumor targeting.

Transferrin Receptor (TfR)

TfR is overexpressed in most BC, including precancerous ductal carcinoma in situ (DCIS).[106] Lactoferrin (LF), a cationic glycoprotein found in mammals and classified within the transferrin protein group, exhibits precise tumor-targeting capabilities through receptor-mediated cellular uptake. Its mechanism involves high-affinity interactions with multiple membrane receptors, particularly low-density lipoprotein (LDL) and TfR, that are abundantly expressed on malignant cell surfaces. This receptor-specific binding promotes efficient intracellular delivery of LF, demonstrating significant specificity toward cancerous tissues.[107,108] Mona et al[85] successfully coupled DTX and Celastrol (CST) with LF to form a novel LF two-drug nanoconjugate (DTX-LF-CST nanoconjugate). LF has a tumor-targeting effect and binds to the LF receptor overexpressed on MCF-7 cells via receptor-mediated endocytosis, resulting in a significant enhancement of cellular uptake and a significant increase in the efficiency of cellular internalisation of the DTX-LF-CST nanoconjugate. The DTX-LF-CST nanoconjugate significantly inhibited tumor growth and prolonged the survival rate of mice.

Glucose Transporter Protein 1 (Glut1) Receptor

Within the family of Glut, the elevated expression of Glut1 is a common finding across various cancer types, such as those of the breast, lung, kidney, colon, and pancreas. Overexpression of Glut1 coincides with its critical role in promoting glucose uptake in breast cancer cells, where it is the predominant glucose transporter in breast cancer cell lines including MCF-7 and MDA-MB-231 cells.[109] Not only does ginsenoside have the potential to replace cholesterol as a liposomal membrane material, ginsenoside liposomes have been found to have strong active tumor cell targeting capabilities.[110] The glucose portion of the hydrophilic part of ginsenoside Rg3 theoretically extends out of the liposome surface, which is a perfect ligand for Glut1 overexpression in BC.[111] Xia et al[86] prepared a multifunctional Rg3 liposome loaded with DTX (Rg3-Lp/DTX). Rg3-Lp/DTX (IC_{50} = 0.12 ng/mL) exhibited enhanced cytotoxicity and apoptosis induction in 4T1 cells compared to DTX (IC_{50} = 6.82 ng/mL). Rg3-Lp/DTX binds more strongly to a limited number of circulating tumor cells (CTC), and Rg3 is recognised by Glut1 to enhance the efficiency of liposome uptake by tumor cells (Figure 3). Glut1 expression exhibits significant variation across different patients and tumor types. Although Rg3 is a natural product, the long-term safety of its liposomal formulation remains unassessed, and systematic studies on its in vivo pharmacokinetics are lacking.

Physicochemical Targeted Drug Delivery System

Physicochemical targeted drug delivery systems are a class of drug delivery systems that use physical or chemical properties to achieve precise release of drugs at specific sites. In the physical stimulus response mechanism, the system releases the drug by making the drug carrier undergo physical changes at a specific site with the help of temperature, magnetic field, and so on. In addition, it can also utilise the response of the drug carrier under specific chemical conditions, such as degradation, dissolution or structural change at specific pH, enzyme concentration or redox potential, to achieve targeted drug release. This precise drug delivery can not only deliver drugs to the lesion site efficiently, but also achieve on-demand drug release according to the characteristics of the microenvironment of the lesion, thus improving the efficacy of the drug while minimising the damage to normal tissues, and providing a safer and more effective solution for the treatment of diseases (Table 4).

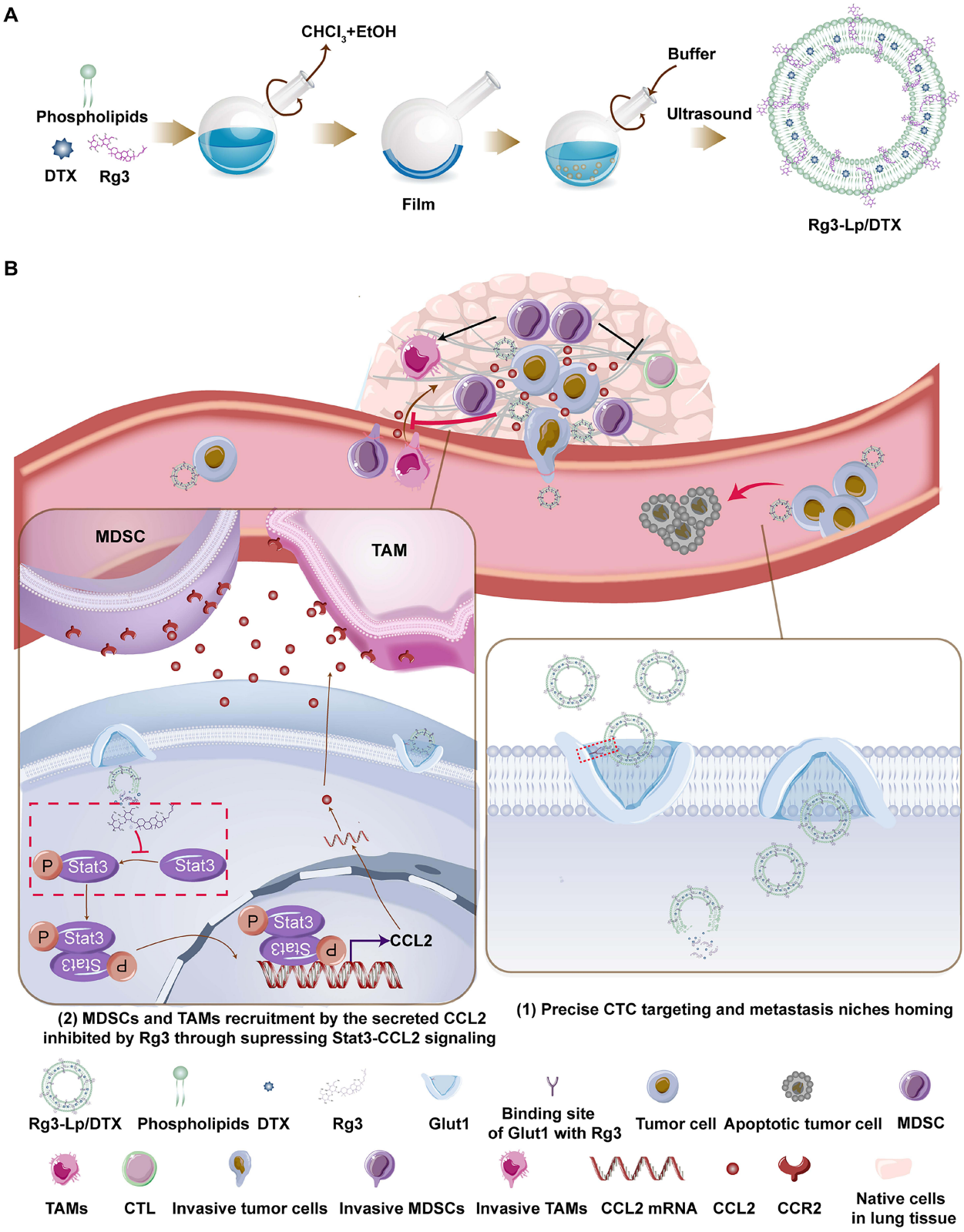

Figure 3 Schematic diagram of Rg3-Lp/DTX preparation and its inhibiting mechanism on lung metastasis of TNBC. (**A**) Preparation of Rg3-Lp/DTX by thin-film hydration method. (**B**) Because Rg3 extends its glucose moieties out of the surface of the liposome, Rg3-Lp/DTX can accurately capture CTCs through Glut1-Rg3 interaction. After reaching metastatic lesions with the disseminated CTCs, Rg3 can inhibit C-C chemokine ligand 2 (CCL2) secretion of tumor cells and thus prevent the recruitment of MDSCs and TAMs, destroy the formation of MNs, and promote the immune surveillance of tumor cells by cytotoxic T lymphocytes (CTLs). Reproduced with permission from Xia J, Ma S, Zhu X, et al. Versatile ginsenoside Rg3 liposomes inhibit tumor metastasis by capturing circulating tumor cells and destroying metastatic niches. *Sci Adv.* 2022 Feb 11;8(6):eabj1262. [86]

Table 4 Physicochemical Targeted Drug Delivery System for DTX

Drug Delivery System	Stimulus-Response Properties	Pharmacokinetics/Tissue Distribution/Efficacy	Year, Ref.
DCF-NP	Magnetic-responsive.	Cytotoxicity (MCF-7 and MDA-MB-231 cells): DCF-NP > DTX. Cellular uptake↑.	2020[112]
DIONP	Magnetic-responsive.	MCF-7 cells viability (%): DIONP < DTX; Pharmacokinetic: AUC↑; MRT↑; $t_{1/2}$↑.	2019[113]
Au/Fe3O4/PVA-10% DTX	Magnetic-responsive.	Cellular Uptake of MCF-7 cells: Au/Fe_3O_4/PVA-10%DTX > DTX; The tumor inhibition: Au/Fe_3O_4/PVA-10%DTX+NIR > Au/Fe_3O_4/PVA-10%DTX.	2020[114]
DTX loaded PNIPAAm-b-PLA nanomicelles	Temperature-responsive.	Cell Viability of MCF-7 cell lines: PNIPAAm-b-PLA > DTX > PNIPAAm-b-PLA loaded DTX; At 37°C for 96 hours the cumulative release was 28.63%; at 40°C the cumulative release reached 42.61%.	2022[115]
pHS-LPHNPs-DTX	pH-sensitive.	Cytotoxicity (MDA-MB-231 and MCF-7 cells): DTX < LPHNPs-DTX < pHSLPHNPs-DTX; Cellular uptake: DTX < LPHNPs-DTX < pHSLPHNPs-DTX; Pharmacokinetic: AUC↑; MRT↑; $t_{1/2}$↑.	2021[116]
[DD]CCNpH-T	pH-sensitive.	Cytotoxicity (MCF-7R cells): [DD]NpH-T > [DD]NP-T > DD; Pharmacokinetic: C_{max}↑; AUC↑; $t_{1/2}$↑; The average weight of the tumors: [DD]NpH-T NPs < [DD]NP-T < DD < DSF < DTX.	2023[117]
PAHD	pH-sensitive.	In vivo Anti-Tumor: TIRs: PAHD > PHD > AHD; Cytotoxicity: PAHD > AHD > HS-DTX > ASP > PHS; Pharmacokinetic: AUC↑; $t_{1/2}$↑.	2019[118]
DTX-loaded HEP-CA-TOC micelles	pH-sensitive.	Cytotoxicity: (MCF-7 and 4T1 cells): DTX-loaded micelles > DTX; Pharmacokinetic: AUC↑, MRT↑, $t_{1/2}$↑.	2020[119]
DTX/RGD NPs	Redox-sensitive.	Cellular uptake of 4T1 cells: DTX/RGD NPs > DTX; Cytotoxicity on 4T1 cells: RGD NPs > NPs > DTX; The TIR in 4T1 tumor-bearing mice: DTX/RGD NPs > DTX.	2023[120]
cRGDfC-NG-DTX	Redox-sensitive.	Cell viabilities (MDA-MB-231 cells): cRGDfC-NG-DTX+GSH < cRGDfC-NG-DTX < DTX < NG-DTX.	2023[121]
DTX@PBDBM NPs	Redox-sensitive.	Apoptosis rates of 4T1 cells: PBDBM NPs: 22.29%, DTX@PBDBM NPs: 49.06%, DTX: 45.18%; Tumor suppression rates: DTX@PBDBM NPs > DTX > PBDBM NPs > PBS.	2023[122]
DTX-loaded DPSP NPs	Redox-sensitive.	4T1 cells: DTX-loaded DPSP NPs: IC_{50} = 15.2 ± 0.9 lg/mL, DTX: IC_{50} = 17.6 ± 1.6 lg/mL.	2022[123]
DTX-loaded micelle-forming MeO-PEG-b-(NIPAAm-co-PBAE) nanoparticles	Redox-sensitive.	Cytotoxicity (MDA-MB-231 cells): DTX-loaded NPs (IC_{50} = 0.20 ± 0.02 μg/mL) > DTX (IC_{50} = 0.3441 ± 0.04 μg/mL); Apoptosis: DTX-loaded NPs (71.5 ± 2.8%) > DTX (42.34 ± 3.1%).	2024[124]
DTX-loaded MST@PBAS NPs	Redox-sensitive.	Cytotoxicity (4T1 cells): DTX-loaded MST@PBAS NPs (IC_{50} = 1.5 μg/mL) > free DTX (IC_{50} = 7.5 μg/mL); Apoptosis rates of 4T1 cells: DTX-loaded MST@PBAS NPs (59.8%) > free DTX (44.7%).	2024[125]

Abbreviations: C_{max}, maximal concentration; AUC, area under the curve; MRT, mean residence time; $t_{1/2}$, half-life; TIR, tumor inhibition rate; ↑, increase; >, greater than; <, less than.

Magnetic-Responsive

Magnetic nanoparticles (MNPs) have high magnetic moments and surface area-to-volume ratios, making them attractive for cancer thermotherapy and targeted drug delivery.[126] These properties enable magnetic nanoparticles to respond efficiently to external magnetic fields, resulting in precise drug delivery and local release, significantly reducing drug distribution in non-target tissues, thereby minimising side effects and improving therapeutic efficacy. In addition, the low toxicity of magnetic nanoparticles further enhances their value in biomedical applications, making them of interest in numerous fields, especially in cancer therapy.[127,128] Panda et al[112] successfully prepared DTX-loaded cobalt ferrite nanoparticles (DCF-NP). The saturation magnetisation values of DCF-NP were 13.74 and 15.13 emu/g at 300 K and 150 K, respectively, which was attributed to the presence of polymer shell on the surface of DCF-NP. In addition, DCF-NP exhibited a smaller hysteresis loop at 300 K, which indicated that the nanoparticles were ferromagnetic. DCF-NP showed effective uptake and antiproliferative efficiency in MCF-7 and MDA-MB-231 cells. However, conducting in vitro studies without establishing tumor mouse models precludes the assessment of DCF-NP's in vivo pharmacokinetic properties. Consequently, it remains uncertain whether magnetic targeting technology can achieve tumor site enrichment in vivo, nor can its pharmacokinetic advantages over free DTX be compared. Panda et al[113] encapsulated iron oxide nanoparticles (IONP) with DTX drug in poly (D, l-lactic-hydroxyacetic) acid (PLGA)-PEG to form DTX-loaded iron oxide nanoparticles (DIONP). The synthesized ionic particles were superparamagnetic at room temperature at a saturation magnetization intensity of 71.9 emu/g and were capable of targeted delivery by external magnetic field. DIONP possessed high saturation magnetization intensity and good drug loading capacity. DIONP showed higher internalization efficiency and better cytotoxicity than free drug to MCF-7 cells. However, no in vitro or in vivo targeting experiments were conducted in the absence of an external magnetic field. Only pharmacokinetic studies were completed, and no tumor-bearing mouse model was established. Consequently, it was impossible to evaluate DIONP's tumor enrichment, tumor inhibition rate, or tissue distribution. Relying solely on in vitro cytotoxicity and pharmacokinetic parameters fails to comprehensively reflect its therapeutic value in vivo. Taheri et al[114] developed a multifunctional nanocarrier Au/Fe_3O_4/PVA-10%DTX using a polyvinyl alcohol (PVA) gel network, combined with gold nanoparticles (AuNPs) and magnetic nanoparticles (Fe_3O_4), which is superparamagnetic and capable of targeted delivery via an external magnetic field. Its maximum saturation magnetisation strength of 30 emu/g is sufficient to support magnetic targeting. In MCF-7 cells, Au/Fe_3O_4 /PVA-10%DTX showed significant cytotoxicity, whereas it had less effect in normal cells, suggesting that the material has good tumor cell selectivity. Au/Fe_3O_4/PVA-10%DTX and the applied magnetic field showed significant growth inhibition (TIR: 70%) in MCF-7 hormonal cells.

Temperature-Responsive

Temperature-responsive PMs consist of macromolecules with heat-sensitive blocks whose solubility in aqueous media can change considerably, thus destabilising PMs and facilitating drug delivery. Poly(N-isopropylacrylamide) (PNIPAAm) is one of the most common temperature-responsive smart materials, showing a strong phase transition in aqueous solution at 32–34 °C, ie, the lower critical solution temperature (LCST).[129,130] In temperature-sensitive PMs based on PNIPAAm, the PNIPAAm can act as a core or corona, as appropriate, depending on the attachment of lipophilic or hydrophilic blocks. These PMs are mainly generated by coupling PNIPAAm with lipophilic segments, where PNIPAAm acts as a hydrophilic shell, utilising its increased hydrophobicity at temperatures above LCST to facilitate micelle dissociation and drug release.[131,132] Ghasemi et al[115] prepared thermo-responsive poly (n-isopropylacrylamide-b-dodecyl acrylate) (PNIPAAm-b-PLA) amphiphilic block copolymers and encapsulated DTX in self-assembled nanomicelles. Drug release experiments showed that the drug release from PNIPAAm-b-PLA/DTX was temperature sensitive. The release was slow at 37 °C (below LCST), with a cumulative release of 28.63% in 96 hours, while the release was accelerated at 40 °C (above LCST), with a cumulative release of 42.61% in 96 hours. In vitro cellular experiments showed that PNIPAAm-b-PLA/DTX had high cytotoxicity against MCF-7 cells. However, this research remains confined to in vitro studies, with no animal models yet established to validate its in vivo efficacy and long-term stability in response to temperature changes. Furthermore, the maximum drug release rate is only approximately 42%, with a significant portion of the drug remaining unreleased, which may compromise its therapeutic efficacy.

pH-Sensitive

pH-sensitive nanocarriers are able to remain stable at physiological pH (near-neutral 7.4) and do not readily release the encapsulated drug. However, when these nanocarriers reach the tumor tissue, the structure of the carrier changes as the tumor tissue is usually acidic (pH around 6.5 to 6.8), the carrier structure undergoes specific dissociation or conformational change. This ultimately facilitates sustained drug release within the acidic tumor microenvironment, thereby minimising adverse effects on healthy tissues.[133,134] pH-sensitive nanocarriers include a variety of types such as nanoparticles and nanomicelles. Jadon et al[116] prepared DTX-encapsulated pH-sensitive LPHNPs (pHS-LPHNPs-DTX). The release of DTX was higher at lower pH 5.5 conditions (42%) compared to only 20% at higher pH 7.4 conditions. This suggests that pH-LPHNPs are pH-sensitive and capable of releasing the drug more rapidly in acidic environments. In vitro cytotoxicity studies showed that pHS-LPHNPs-DTX exhibited higher cytotoxicity and cellular uptake efficiency in MCF-7 and MDA-MB-231 cells compared to free DTX and LPHNPs-DTX. In addition, pHS-LPHNPs-DTX exhibited significant breast tumor growth inhibition. Swetha et al[117] prepared DTX and disulfiram (DSF) loaded pH sensitive NPs ([DD]NpH-T). [DD]NpH-T showed a faster drug release rate at pH 6.8 than pH 7.4, suggesting that it is unstable in acidic environments and is capable of releasing drugs. Compared to [DD]NP-T and DD, [DD]NpH-T significantly reduced MCF-7R cell viability, significantly increased cytotoxicity and higher cellular uptake. [DD]NpH-T showed significant anti-tumor effects in in vivo experiments, including reduction in tumor volume, reduction in tumor weight, increase in intra-tumor apoptosis and reduction in lung metastases. Liu et al[118] constructed a DTX/aspirin (ASP) nanocomplex (PAHD) based on heparin sulphate (HS) and cationic polyethyleneimine (PEI)-PEG. PAHD showed efficient cellular uptake at pH 6.8, whereas it was weaker at pH 7.4, and the results suggest that PAHD favours cellular uptake under weak acidic conditions. The toxicity of PAHD to MCF-7 cells was significantly higher at pH 6.8 than at pH 7.4, whereas it showed lower toxicity in normal breast epithelial cells, MCF-10A. In addition, PAHD showed significant effects in inhibiting tumor growth (TIR: 92.2%) and lung metastasis. Emami et al[119] developed pH-sensitive polymeric micelles loaded with DTX consisting of TOC and heparin (HEP), named DTX-loaded HEP-CA-TOC micelles. At pH 5.5, the release rate of DTX was significantly higher than that at pH 7.4, indicating that the micelles were able to release the drug rapidly in an acidic environment. Compared to free DTX, the HEP-CA-TOC micelles enhanced DTX accumulation within MCF-7 and 4T1 cells, exhibiting greater cytotoxicity towards both cell types. The study precisely controlled pH in vitro using buffers; however, the pH within the tumor microenvironment in vivo is subject to interference from multiple factors. Consequently, the "rapid release" observed at pH 5.5 in vitro does not necessarily indicate that the compound retains selectivity within the complex physiological environment. The research was limited to pharmacokinetic experiments and did not validate tumor suppression rates or survival prolongation effects in tumor-bearing mice.

Redox-Sensitive

Redox-sensitive nanoparticles are a special class of drug carriers that respond to and release encapsulated drugs under specific redox conditions. Tumor tissues have a higher concentration of glutathione (GSH) in the cytoplasm compared to normal tissues, and this high concentration of GSH cleaves specific chemical bonds in the nanoparticles via a thiodisulfide exchange reaction, thus ensuring that redox-sensitive nanoparticles release drugs in specific tissues.[135] Yao et al[120] prepared pH/ROS dual-responsive NPs (DTX/RGD NPs) loaded with DTX. DTX was completely released from the nanoparticles at pH 5.0/1.0 mM H_2O_2, indicating that the carrier was severely damaged under the combined effect of acidic environment and ROS, thus allowing the complete release of DTX. Compared with free DTX, DTX/RGD NPs significantly reduced the activity of 4T1 cells, exhibited stronger anti-tumor activity and cytotoxicity, and significantly inhibited tumor growth (Figure 4). Altinbasak et al[121] developed a redox-responsive nanogel loaded with DTX based on thiol-maleimide and thiol-disulfide exchange chemistry. The nanoparticles were capable of degrading and releasing their encapsulated drug in an acidic reducing (pH 5.5, 10 mM GSH) environment. The cell-targeting peptide-conjugated nanogels exhibited preferential cell internalisation and enhanced cytotoxicity in glutathione-rich BC cells, and cell viability was significantly reduced. However, no animal model was established to validate tumor targeting, distribution, efficacy, and toxicity, leaving a lack of in vivo data to support preclinical translation. Zhang et al[122] developed a novel one-step oxidative polymerisation method based on 1,4-butanediol bis (mercapto) acetate (BDBM) for the synthesis of redox-responsive polybisdisulphide compounds (PBDBM), which were loaded with DTX to form NPs (DTX@PBDBM NPs). Under 10 mM GSH conditions,

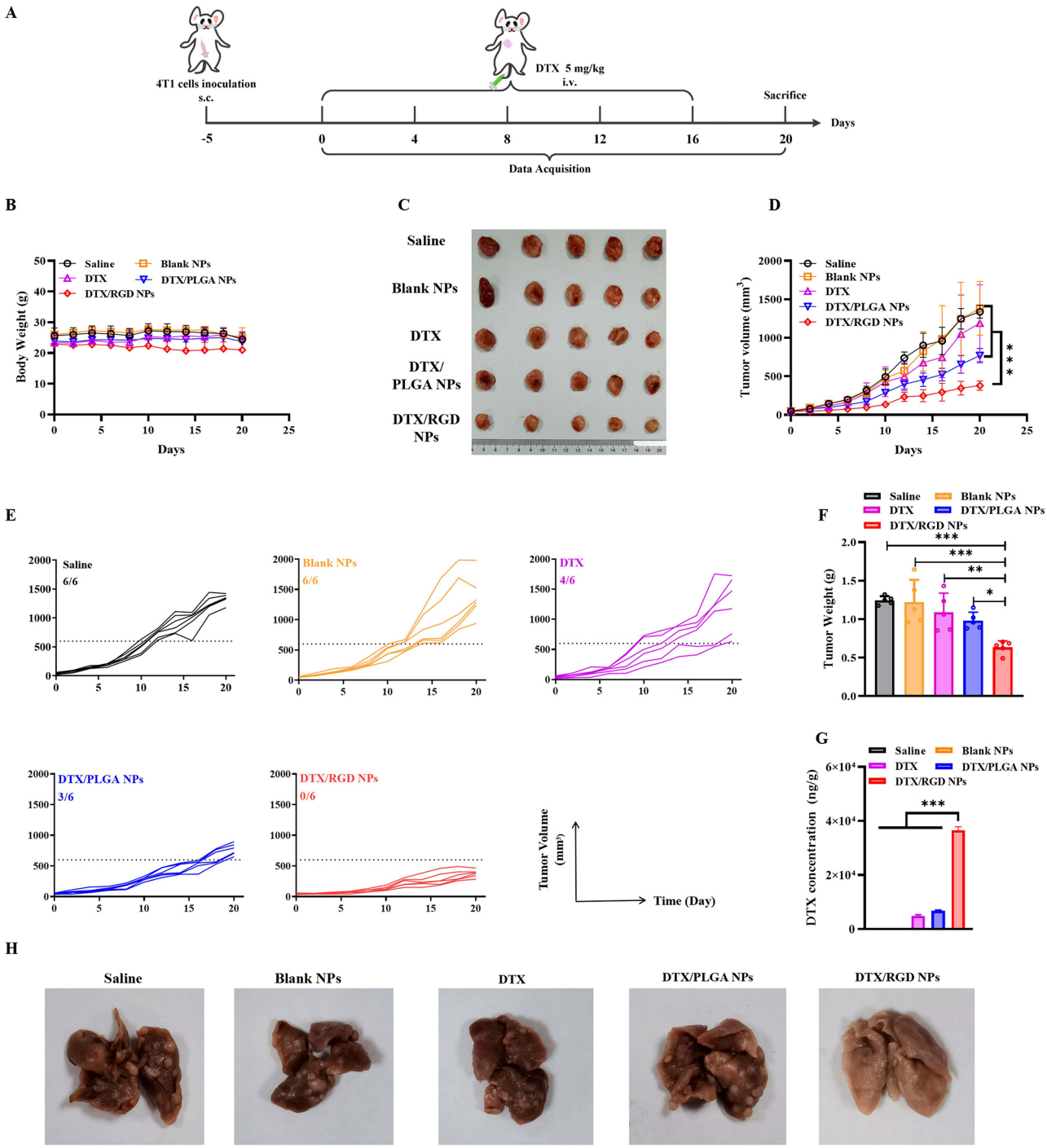

Figure 4 In vivo antitumor efficacy evaluation of blank NPs, DTX and various DTX-loaded NPs in 4T1 tumor-bearing mice. (**A**) The administration time after tumor inoculation. Mice received 5 mg/kg of DTX or 5 mg/kg of various DTX-loaded NPs via vein every four days for five times. (**B**) The body weight changes of mice following different treatment (n = 6). (**C**) Representative photographs of tumor tissues of mice following different treatment. (**D**) The tumor growth curves of mice following different treatment (n = 6). (**E**) Individual tumor volumes of mice following different treatments. The ratio refers to the proportion of mice with tumors that exceed 600 mm3 on day 20. (**F**) The tumor weight of mice following different treatments. (**G**) The DTX concentration in tumor tissues of mice following different treatments (n = 3). (**H**) The photo images of collected lungs in the mice following different treatments on day 20. *, statistically different at $p < 0.05$; **, statistically different at $p < 0.01$; ***, statistically different at $p < 0.001$, compared with DTX/RGD NPs. Reproduced from Yao P, Wang X, Wang Q, et al. Cyclic RGD-Functionalized pH/ROS Dual-Responsive Nanoparticle for Targeted Breast Cancer Therapy. *Pharmaceutics*. 2023 Jun 26;15(7):1827.[120] © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

https://doi.org/10.2147/IJN.S540777

DTX@PBDBM NPs underwent degradation and aggregation at high GSH levels, releasing the drug DTX. DTX@PBDBM NPs exhibited a better potential to induce apoptosis and cell-cycle blockade compared to free DTX and significantly inhibited tumor growth (TIR: 54.4%), while attenuating the systemic toxicity of DTX. Shi et al[123] successfully prepared novel redox-sensitive nanoparticles (DPSP NPs) loaded with DTX by coupling polycaprolactone with disulfide-linked polyethylene glycol (DDMAT-mPEG-S-S-PCL, DPSP). DPSP NPs were able to disassemble the nanoparticles at pH 7.4 and 10 mM GSH, which promoted drug release. DTX-loaded DPSP NPs exhibited stronger cytotoxicity in 4T1 cells compared to free DTX. In addition, the presence of GSH was able to enhance the anti-tumor cell activity of DTX, resulting in DTX-loaded DPSP NPs showing significant tumor inhibitory effects in both in vitro and in vivo experiments. Badparvar et al[124] developed a novel pH/redox-responsive hyperbranched MeO-PEG-b-(NIPAAm-co-PBAE) NPs loaded with DTX. The release of DTX reached 95% within 24 h at pH 6.4 and 10 mM GSH, demonstrating that this nanoparticle is capable of specifically releasing drugs in the TME. DTX-loaded NPs exhibited significantly higher cytotoxicity, cellular uptake and induced significantly higher apoptosis in MDA-MB-231 cells compared to free DTX. However, all experiments were confined to the in vitro cellular level and lacked validation in animal models. It remains unclear whether targeted penetration can be achieved in vivo through size contraction and charge reversal. Furthermore, significant discrepancies may exist between in vitro TME simulations and the actual in vivo microenvironment (Figure 5). Taghipour et al[125] engineered poly (β-amino ester) (PBAS) micelles loaded with DTX and featuring dual pH/redox responsiveness. These micelles were modified using chimeric peptides and CD44 aptamer (TA1), resulting in the formation of DTX-loaded MMP-9 sensitive heptapeptide/TA1 aptamer-modified poly (β-amino ester) (MST@PBAS) micelles. Under high GSH and low pH conditions, this nanoparticle undergoes disruption, which

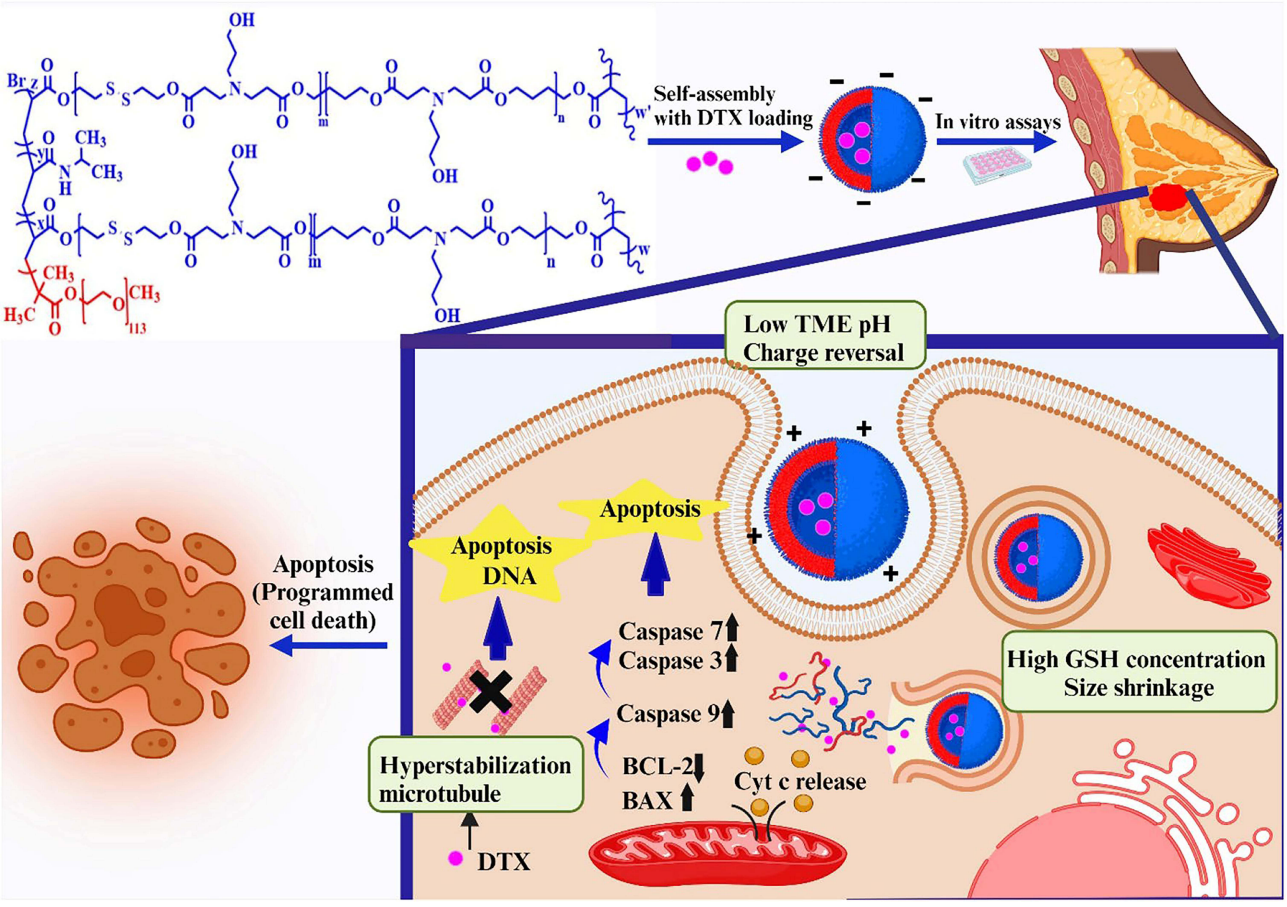

Figure 5 Graphical representation showing the size and charges reversible smart pH/redox dual-stimuli hyperbranched MeO-PEG-b-(NIPAAm-co-PBAE) nano-vehicle for promoted breast cancer tumor targeting and dual pH/redox triggered DTX release. Reproduced with permission from Badparvar F, Marjani AP, Salehi R, Ramezani F. Dual pH/redox-responsive hyperbranched polymeric nanocarriers with TME-trigger size shrinkage and charge reversible ability for amplified chemotherapy of breast cancer. *Sci Rep*. 2024 Apr 12;14(1):8567.[124] Creative Commons Attribution 4.0 International License. Copyright © 2024 by the authors.

significantly increases the release of DTX. DTX-loaded MST@PBAS micelles showed higher cytotoxicity and higher cellular uptake. In a 4T1 hormonal Balb/c mice model, the use of only 1/10th of the dose of DTX-loaded MST@PBAS micelles equivalent to that of free DTX significantly inhibited tumor growth and produced larger areas of necrosis and apoptosis in the tumor tissue.

Co-Delivery Drug Delivery System

Co-delivery drug systems are advanced drug delivery strategies designed to deliver two or more drugs simultaneously to achieve synergistic therapeutic effects, reduce drug dosage, decrease side effects, and improve treatment outcomes. In recent years, the concurrent administration of multiple drugs in combination therapy has demonstrated superior efficacy compared to the use of a single drug for treatment.[136] Numerous studies have demonstrated that nanoplatform-based DTX, when combined with photothermal therapy, gene therapy, chemotherapeutic agents, and active ingredients of traditional Chinese medicines (TCM), can enhance the inhibitory effect on tumor cells, while effectively reducing the incidence of adverse effects and addresses the issue of drug resistance in tumor cells (Table 5).

Co-Delivery Photothermal Therapy

Photothermal therapy (PTT) is a very effective and non-invasive therapy for the treatment of many types of cancers, and the combination of PTT with other drugs can increase the sensitivity of the tumor to temperature.[153] The use of photothermal converting agents or photosensitisers in PTT absorbs energy and generates heat when irradiated by a certain wavelength of near infrared (NIR) light, which can be effective in eradicating tumor cells. The application of nano-drug delivery technology assisted by NIR light enhances interstitial permeation and improves drug delivery, resulting in enhanced cell permeability and significant inhibition of tumor cell growth.[154] Liu et al[137] successfully prepared multifunctional nanoplatforms (HPDC NPs) by loading DTX and perfluorohexane (PFH) CNs and combining them with poly (lactic-hydroxyglycolic acid) (PLGA) nanoparticles modified with anti-hypoxia-inducible factor 1α (HIF 1α) antibody. Under near-infrared light irradiation, the CNs were able to generate a photothermal effect, which could trigger the rupture of the HPDC NPs for efficient drug release. Compared with chemotherapeutic drugs or photothermal therapy alone, HPDC NPs under NIR light irradiation can significantly improve the killing effect on tumor cells. In addition, HPDC NPs can significantly inhibit the growth of tumor cells, which is superior to chemotherapy or photothermal therapy alone (Figure 6). Demonstrated significant advantages in both in vitro and in vivo experiments, yet remains constrained by challenging temperature control and elevated risks of normal tissue damage. Furthermore, as carbon-based nanomaterials, CNs exhibit extremely slow degradation rates in physiological environments, predisposing them to prolonged accumulation within lymph nodes. Liu et al[138] developed a quadruple-functionalised poly(dopamine)-modified polymeric nanoplatform, DTX/NPs@PDA/DOX-PEG-Apt, which has been engineered for dual loading of the hydrophobic drug DTX and the hydrophilic drug doxorubicin (DOX), enabling targeted drug delivery. After irradiation at an intensity of 1.5 W/cm^2 for 5 min, the release of DTX increased by about 10–15%. DTX/NPs@PDA/DOX-PEG-Apt +NIR (IC_{50} = 0.38 μg/mL) exhibited significant cytotoxicity compared to DTX (IC_{50} = 13.29 μg/mL) and DTX/NPs@PDA/DOX-PEG-Apt (IC_{50} = 0.55 μg/mL), and the co-delivery treatment effectively improved the cancer cell killing effect. In addition, the tumor growth in mice was almost completely inhibited by DTX/NPs@PDA/DOX-PEG-Apt, and the tumor volume was even significantly reduced after NIR irradiation.

Co-Delivery Gene Therapy

RNA interference (RNAi) technology, an endogenous mechanism that brings about gene silencing at the post - translational stage by leveraging small interfering RNAs (siRNAs) or microRNAs (miRNAs), has emerged as a novel and promising approach for cancer treatment.[155] SiRNA's technology has shown novel potential for novel diagnostic and therapeutic innovations with a variety of cancer interventions, and a variety of experiments have demonstrated that the combined use of natural products and siRNAs is able to overcome drug resistance and improve therapeutic efficacy.[156] Behiye et al[139] prepared nanolipid carriers (NLCs) for co-delivery of siRNA and DTX. The prepared lipid nanoparticle formulation is more toxic to MCF-7 cells compared to pure DTX (IC_{50} = 3.28 ± 0.39 μg/mL) and tessoderm (IC_{50} = 2.38 ± 0.11 μg/mL). This finding demonstrated that the inclusion of siRNA notably augmented the cytotoxicity. It implied that

Table 5 Co-Delivery Systems for DTX Combined with Other Drugs

Drug Delivery System	Drug	In vitro and in vivo Model	Antitumor Effect and Mechanism	Year, Ref.
HPDC NPs	CNs 10 mg + DTX 2mg.	In vitro: Walker256 cells In vivo: Walker256 tumor cells.	The cellular apoptosis rate: HPDC NPs (82.31%) > HPC NPs (31.76%) > DTX (25.24%); Cell apoptosis: HPDC NPs + laser > HPC NPs + laser > DTX.	2021[137]
DTX/NPs@PDA/DOX-PEG-Apt	CA-PLGA: 100 mg + DTX: 10 mg.	In vitro: MCF-7 cells, In vivo: MCF-7 cells xenograft-bearing mice model.	In vitro cytotoxicity↑; Cellular uptake↑; Tumor weight: drug-free NPs@PDA-PEG-Apt > DTX+DOX > DTX/NPs@PDA/DOX-PEG > DTX/NPs@PDA/DOX-PEG-Apt > DTX/NPs@PDA/DOX-PEG-Apt+NIR.	2019[138]
siRNA-cF2-DTX	DTX: 5mg/mL + siRNA.	In vitro: MCF-10A and MCF-7 cells.	Cytotoxicity: siRNA-cF2-DTX > cF2-DTX > DTX > Taxotere®.	2024[139]
DTX/miR-34a nanoplexes	miR-34a + DTX.	In vitro: 4T1 and MDA-MB -231 cells.	Cytotoxicity and apoptosis (4T1 and MDA-MB-231 cells): FA-DTX-miR-34a NPs > DTX-miR34a NPs > FA-DTX/NC-miRNA NPs > DTX NC-miRNA NPs > DTX NPs > DTX.	2021[140]
DTX-lipoplex	SIRT1 shRNA + DTX.	In vitro: MDA-MB-231 and MCF-7 cells; In vivo: DMBA induced animal breast cancer model.	In vitro cell cytotoxicity: DTX-lipoplex > DTX; Apoptotic potential: DTX-lipoplex (1.06) > DTX-liposome (0.82) > DTX (0.57); % Tumor volume reduction: DTX-lipoplex (~78%) > DTX-liposome (~52%) > shRNA-lipoplex (~35%).	2021[141]
(DTX+CUR)-loaded mixed micelles	DTX and CUR = 0.5: 0.5.	In vitro: MCF-7 and MCF-7/ADR cells; In vivo: MCF-7/ADR tumors model.	Cytotoxicity (MCF-7 and MCF-7/ADR cells): (DTX +CUR)-loaded mixed micelles > DTX-loaded mixed micelles > DTX-loaded micelles; Apoptosis rates (MCF-7/ADR cells): (DTX+CUR)-loaded mixed micelles (60.97 ± 3.14%) > DTX-loaded mixed micelles (59.75 ± 3.85%) > DTX-loaded micelles (5.28 ± 1.25%) > pure (DTX+CUR) (4.30±0.94%).	2024[142]
CUR-DTX liposomes	CUR (2 mg) + DTX (4 mg).	In vitro: MCF-7 cells; In vivo: MCF-7 tumor-bearing nude mice model.	Cytotoxicity (MCF-7 cells): CUR-DTX-L > CUR > DTX-L > DTX; Anti-tumor efficacy of tumor-bearing mice: CUR-DTX-L (TIR: 66.23%) > CUR-DTX (TIR: 54.03%) > DTX-L (TIR: 50.80%) > CUR-L (TIR: 37.52%).	2022[143]
DxTq-LNCs	DTX: THQ = 1:2.	In vitro: MCF-7 and MDA-MB -231 cells; In vivo: female Balb/c mice model.	% Cell inhibition of MCF-7 cells: DxTq-LNCs > DTX-LNCs (76.35 ± 2.80%) > DTX (50.12 ± 2.88%); The average tumor volume: DxTqLNCs (709.6 ± 91.2 mm^3) < DTX (1588.1 ± 199.4 mm^3) < control (1999.2 ± 285.3 mm^3); Apoptosis↑.	2020[144]
DTX/THQ CLNCs	DTX + THQ + CLNCs.	In vitro: MCF-7 and MDA-MB -231 cells.	% Inhibition of the MCF-7 cells: CLNCs > ULNCs > DTX-LNCs; % Inhibition of the MDA-MB-231 cells: CLNCs (87.2 ± 1.5%) > ULNCs (74.6 ± 3.1%) > DTX-LNCs (70.3 ± 1.1%).	2020[145]
(DTX+TQ) B-NE	DTX + TQ + B-NE.	In vitro: MCF-7 and MDA-MB -231 cells.	Cytotoxicity (MCF7 and MDA-MB-231 cells): (DTX+TQ) B-NE > DTX > DTX+TQ > B-NE>TQ; The rates of early apoptotic MCF-7 cells: (DTX+TQ) B-NE (67.53 ± 0.60%) > B-NE (54.97 ± 0.65%);	2020[146]

DTX/DHA NPs	DTX: DHA = 2.75:1.	In vitro: 4T1 cells; In vivo: Orthotopic 4T1 breast cancer model.	The apoptotic rates (4T1 cells): D/D NPs (23.5%) > Free D/D (18.4%) > DTX NPs (16.5%) > DTX (15.2%); The tumor growth inhibition rates: D/D NPs (84.3%) > DTX NPs (56.0%) > Free D/D (54.9%) > DTX (48.4%).	2020[147]
CV-DTX-S-SNEDDS	DTX + CV-L-SNEDDS.	In vitro: MDA-MB-231 cells.	Cytotoxicity in MDA-MB-231 cells: CV-DTX-S-SNEDDS > CV-loaded SNEDDS > DTX-loaded SNEDDS > Free DTX; Quantity of apoptotic cells↑.	2023[148]
DOX-DTX-DMN	50 mg DOX + 30 mg DTX.	In vivo: Female athymic nude mice model.	Tumor volume↓; % Survival of the animals: DOX-DTX-DMN (100%) > DOX-DTX-injection > DOX-injection.	2019[149]
mPEG-PMLA-DOX /DTX	DOX + DTX + mPEG-PMLA.	In vitro: MDA-MB-231 cells; In vivo: Balb/c nude mice model.	Apoptosis rate of MDA-MB-231 cells: mPEG-PMLA-DOX/DTX (78.8%) > mPEG-PMLA-DTX > mPEG-PMLA-DOX > DTX > Control; Tumor volume: mPEG-PMLA-DOX/DTX < DOX+DTX < mPEG-PMLA.	2020[150]
D/P-NCs	DTX: PIC = 2:1.	In vitro: MCF-7/HER2 and MCF-7 cells; In vivo: MCF-7/HER2 tumor-bearing mice model.	Cytotoxicity (MCF-7/HER2 cells): D/P-NCs > DTX > PIC; Pharmacokinetics: AUC↑; $t_{1/2}$↑; Inhibition of tumor growth: Tra-D/P_NC, Per-D/P_NC, Dual-D/P_NC > PIC > DTX	2022[151]
Nanoparticles co-delivering SAL and DTX	SAL: DTX = 1:1.	In vitro: MCF-7 and MCF-7-MS cells; In vivo: MCF-7 cells derived subcutaneous tumor model.	Cytotoxicity (MCF-7 cells): NSD > NS+ND > SAL+DTX > DTX > SAL; Tumor inhibitory rate: NSD (77.70 ± 4.92%) > NS+ND (66.89 ± 6.56%) > SAL+DTX (61.80 ± 6.56%) > DTX (46.23 ± 7.38%) > SAL (11.15 ± 13.11%).	2019[152]

Abbreviations: AUC, area under the curve; $t_{1/2}$, half-life; TIR, tumor inhibition rate; ↑, increase; >, greater than; <, less than.

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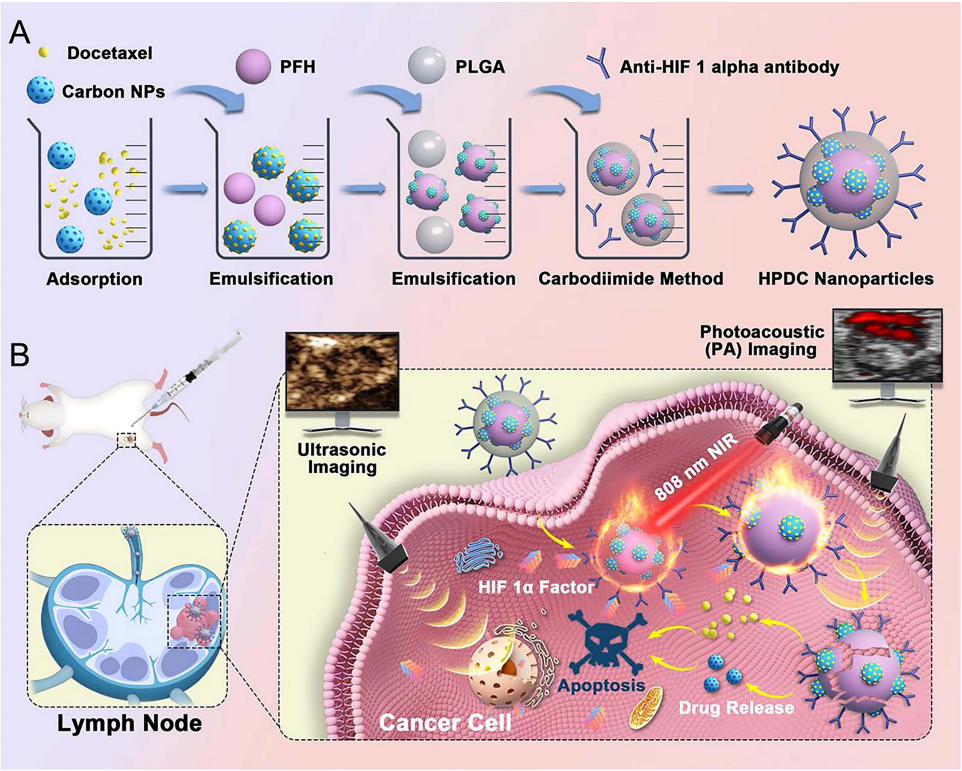

Figure 6 (**A**) Schematic diagram of the manufacturing process of HPDC NPs. (**B**) The corresponding synergistic effect of 808 nm laser-triggered hyperthermia and DOC-mediated chemotherapy. Reproduced with permission from Liu, W, Ye, X, He, L, et al. A novel targeted multifunctional nanoplatform for visual chemo-hyperthermia synergy therapy on metastatic lymph nodes via lymphatic delivery. *J Nanobiotechnol* 19, 432 (2021).[137] Creative Commons Attribution 4.0 International License. Copyright © 2021 by the authors.

the combination of siRNA and DTX exerted a synergistic action, enabling more efficient inhibition of cancer cell growth. Additionally, miRNAs play a crucial role in the progression of breast cancer. miRNA-34a is a potent down-regulated tumor suppressor among a large number of miRNAs analysed, inhibiting tumor growth by targeting multiple genes, inhibiting tumor angiogenesis, inducing apoptosis and blocking prolife ration in cancer cells. The miR-34a nanocomplex has been demonstrated to have great potential to induce apoptosis in both cell lines (MCF-7 and 4T1 cells),[157] improving the efficacy of DTX. Sharma et al[140] developed a folate-targeted hybrid lipid-polymer nanocomplex for co-delivery of DTX and miRNA-34a. Folate-targeted DTX/miR-34a nanocomplexes showed higher cytotoxicity and apoptotic effects than alone in 4T1 and MDA-MB-231 cell lines, with cell viability of 17% and 14%. This result suggests that the co-administration of DTX and miR-34a exerts a remarkable synergistic impact. It is capable of more efficiently suppressing the proliferation of cancer cells and triggering apoptosis. However, miRNA-34a is a multi-target regulatory molecule; in addition to targeting oncogenes, it may also inadvertently affect tumor suppressor genes in normal cells, posing a high risk of off-target effects. Furthermore, miRNAs themselves are prone to degradation, temperature-sensitive, and exhibit poor stability. Moreover, studies have not systematically evaluated their long-term toxicity.

Silent information regulator 1 (SIRT1), the initial member of the Sirtuin family, shows remarkably elevated expression in diverse cancers such as colon cancer, brain cancer, lymphoma, and breast cancer.[158] Short hairpin RNAs (shRNAs) are RNA sequences that form a tight hairpin - shaped turn. They can be cloned into expression vectors, guaranteeing the continuous expression of shRNAs.[159] ShRNAs are able to inhibit the production of SIRT1, which in turn sensitises drug-resistant cells by blocking the expression of efflux transporters.[160,161] Swami et al[141] developed a pH-sensitive cationic liposome for co-delivery of DTX and SIRT1 shRNA, known as DTX-lipoplex. DTX-liposomes were significantly more cytotoxic to MDA-MB-231 and MCF-7 cell lines than DTX alone, with approximately 2.35-fold and 2.54-fold lower IC_{50} values, respectively. In addition, the apoptosis rate of DTX-lipoplex-treated cells was significantly

higher, suggesting a synergistic effect of the combination of DTX and shRNA. In addition, DTX-lipoplex significantly inhibited tumor growth, and tumor volume was reduced by approximately 78%.

Co-Delivery Active Ingredients of Traditional Chinese Medicine

In recent years, combining herbal medicines with chemotherapeutic agents, which act on multiple targets and signaling pathways, has emerged as a novel strategy in tumor therapy. This approach offers enhanced efficacy compared to drugs that target only a single molecule.[162] Curcumin (CUR), a natural polyphenol derived from turmeric, exhibits a range of beneficial biological activities. These include antibacterial, antiviral, anticancer, and antioxidant properties. It has been demonstrated to have preventive and therapeutic effects in various cancers, among which is breast cancer.[163] Dian et al[142] constructed mixed micelles of DTX and CUR. The mixed micelles loaded with both DTX and CUR demonstrated the greatest cytotoxicity towards MCF-7 and MCF-7/ADR cells. Moreover, compared to single-agent formulations, they significantly increased cellular uptake. The (DTX + CUR)-loaded mixed micelles exerted the highest lethality, reaching (60.97 ± 3.14%), against MCF-7/ADR cells, thereby enhancing the therapeutic effect. The micelles loaded solely with DTX could only partially overcome multidrug resistance (MDR), yet this effect was notably augmented when CUR was incorporated. However, this study lacks a thorough assessment of the potential toxicity of the carrier material. While it clearly establishes the pivotal role of CUR in reversing drug resistance, it fails to elucidate the underlying molecular mechanisms in depth. Furthermore, the industrial-scale production and long-term storage stability of the micellar formulation remain unexamined. Ye et al[143] prepared a novel multifunctional liposome (CUR-DTX-L) loaded with CUR and DTX. CUR-DTX-L showed enhanced activity in inhibiting MCF-7 cells proliferation compared with free drug and single drug liposomes (DTX-L, CUR-L). It showed significant anti-tumor effect (TIR: 66.23%) in MCF-7 tumor nude mouse model with significantly smaller tumor volume and weight than other treatment groups.

Thymoquinone (THQ), an active component present in black cohosh essential oil, has demonstrated significant impacts on breast cancer treatment. It functions by regulating apoptosis, halting the cell cycle, and suppressing tumor angiogenesis. THQ has been shown to act synergistically in combination with several anticancer drugs, leading to apoptosis and significantly reducing the growth of BC cells.[164,165] Zafar et al[144] prepared DTX and THQ co-encapsulated lipid nanocapsules (DxTq-LNCs). DxTq-LNCs exhibited significant cytotoxicity against MCF-7 and MDA-MB-231 cells compared to single-agent loaded LNCs. In addition, DxTq-LNCs significantly inhibited the migratory ability of MDA-MB-231 cells and induced apoptosis. DxTq-LNCs inhibited the toxic effects of free drug and increased the maximum tolerated dose (MTD) of the drug. However, the molecular mechanisms by which THQ reverses drug resistance and its impact on DTX pharmacokinetics have not been thoroughly explored. Long-term toxicity, formulation stability, and scalability feasibility remain unexamined. Zafar et al[145] used chitosan grafted lipid nanocapsules (CLNCs) for co-delivery of DTX and THQ. CLNCs showed significant cytotoxicity against MCF-7 and MDA-MB-231 cells compared to free drug and single drug loaded lipid nanocapsules (LNCs) with IC_{50} values of 0.45 μM and 6.62 μM respectively. CLNCs showed greater uptake and stronger anti-tumor effect on MCF-7 breast cancer cells (TIR: 51.8%). This suggests that the combination of THQ and DTX has a synergistic effect, leading to apoptosis and significantly reducing the growth of breast cancer cells. Mayson et al[146] co-encapsulated DTX and THQ in borage oil-based nanoemulsions (B-NE) by ultrasound to obtain (DTX+TQ) B-NE formulations. (DTX+TQ) B-NE achieves precise co-delivery of both drugs via a nanocarrier, resolving the antagonism issues encountered when free drugs are used in combination. Within the B-NE system, the CI values decreased to 0.6 (MCF-7 cells) and 0.9 (MDA-MB-231 cells), respectively. Moreover, only half the dose of DTX (mixed 1:1 with TQ) achieved cytotoxicity equivalent to the full dose of free DTX, significantly reducing the effective therapeutic dose of DTX and laying the groundwork for mitigating clinical toxicity. Furthermore, it can simultaneously activate both apoptosis and autophagy pathways to combat breast cancer cells. However, these studies remain significantly limited: research is confined to the cellular level, lacking animal models, pharmacokinetic data, and toxicity assessments.

Dihydroartemisinin (DHA), which is derived from artemisinin and extracted from the traditional Chinese herb Artemisia annua, has been proposed by the World Health Organization as an alternative option for anti-malarial treatment.[166] Furthermore, research has demonstrated that DHA can trigger both apoptosis and autophagy within cancer cells, thus impeding the progression of breast cancer.[167] Tao et al[147] constructed nanoparticles (D/D NPs) for co-delivery

of DTX and DHA. The apoptosis rates of 4T1 cells treated with DTX, free D/D, DTX NPs and D/D NPs were 15.2%, 18.4%, 16.5%, and 23.5%, respectively, indicating that the synergistic effect of D/D NPs through DTX and DHA significantly increased the apoptosis of 4T1 cells. D/D NPs significantly inhibited the tumor growth of 4T1 cell in situ metastatic breast cancer mice (TIR: 84.3%), enhanced the anti-tumor effect of the drug and reduced the toxicity to normal tissues (Figure 7).

Carvacrol (CV) is a naturally occurring monoterpene phenolic compound that has been shown to significantly inhibit the proliferation of breast cancer MCF-7 cells.[168] Mohd et al[148] successfully achieved the successful development of a novel solid self-nanoemulsifying drug delivery system (S-SNEDDS) co-loaded with DTX and CV. The SNEDDS loaded with CV-DTX brought about a remarkable enhancement in cytotoxic effects when the concentration exceeded 10 μg/mL. The DTX-CV-loaded SNEDDS had a MIC_{50} value 5.2-fold lower than that of free DTX. Additionally, as the concentration of the CV-DTX-S-SNEDDS treatment increased, the number of apoptotic cells rose significantly.

Co-Delivery Chemotherapeutic Agents

Doxorubicin (DOX) and DTX are frequently utilized in synergistic combinations for treating various solid tumors. In clinical practice, they are particularly regarded as first - line therapeutic agents for patients with advanced breast cancer. Bhatnagar et al[149] prepared dissolvable microneedles (DMN) co-delivering DOX and DTX. After treatment with DOX-DTX-DMN, the survival rate of Balb/c mice bearing 4T1 breast cancer cells was 100%, and the DOX and DOX-DTX

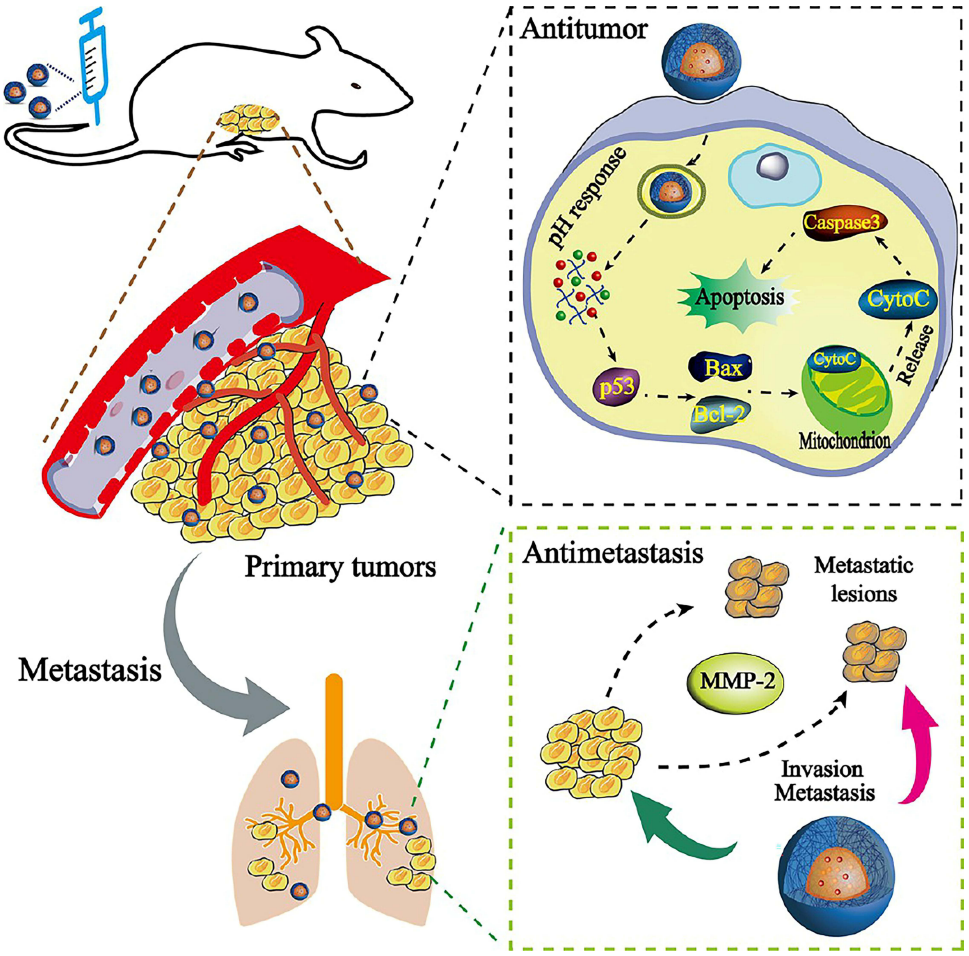

Figure 7 Schematic Illustrations of the Mechanism of D/D NPs Inducing Antitumor and Antimetastasis Effect in Orthotopic Metastatic Breast Cancer. Reproduced with permission from Tao J, Diao L, Chen F, et al. pH-sensitive nanoparticles codelivering docetaxel and dihydroartemisinin effectively treat breast cancer by enhancing reactive oxidative species-mediated mitochondrial apoptosis. *Molecular Pharmaceutics* 18(1) (2020) 74-86. [147] Copyright © 2021 American Chemical Society.

groups had the shortest survival time of 9 and 11 days, respectively. There were more apoptotic cells and higher in vivo tumor suppression in the DOX-DTX-DMN group, and the co-delivery of DOX and DTX was more effective in controlling the growth of tumors than alone. However, this study lacks an assessment of systemic toxicity and pharmacokinetics. Yu et al[150] developed a novel mPEG-poly (β-malic acid) (mPEG-PMLA) nanoparticles co-delivering DOX and DTX to form mPEG-PMLA-DOX/DTX coupling. The mPEG-PMLA-DOX/DTX conjugate manifested a pronounced synergistic inhibitory action. The IC_{50} values for DOX and DTX were measured at 0.62 μg/mL and 0.91 μg/mL respectively. Significantly, these values represented just 40% and 7% of the IC_{50} values of free DOX and DTX. Moreover, in vivo studies, the mPEG-PMLA-DOX/DTX conjugate demonstrated a more robust antitumor efficacy and reduced systemic toxicity in comparison to the combination of free drugs.

Co-Delivery PI3K Inhibitors

The phosphatidylinositol 3-kinase (PI3K) signalling pathway is dysregulated in multiple cancers, including breast cancer, and plays a pivotal role in cell growth, survival, and migration. However, early PI3K inhibitors lacked selectivity, making it difficult to precisely define the contribution of PI3K inhibition to the observed antitumor effects when combined with taxane chemotherapy. Pictilisib (PIC, GDC-0941) is an effective, selective pan-inhibitor of Class I PI3K family members, inhibiting the p110α, p110β, p110δ, and p110γ subunits of PI3K. It has demonstrated favourable antitumor efficacy, safety, and tolerability in clinical trials. The drug is currently undergoing clinical development for solid tumor indications including breast cancer.[169,170] It exhibits preclinical activity in breast cancer cell lines and may potentiate the effects of taxanes, benefiting patients with or without aberrant PI3K pathway activation.[171] It has also been shown that the addition of PIC to DTX or trastuzumab and patulizumab enhances the anti-tumor effects in breast cancer cells.[172] Cheng et al[151] designed nanocarriers (NCs) co-loaded with DTX and PICbioD/P-NCs (IC_{50} = 8.54 ng/mL) co-loaded with DTX and PIC in a 2:1 ratio exhibited significantly enhanced cytotoxicity against MCF-7/HER2 cells compared to DTX (IC_{50} = 12.50 ng/mL) and PIC (IC_{50} = 86.75 ng/mL). In addition, D/P-NCs significantly inhibited tumor growth in MCF-7/HER2 hormonal mouse model, suggesting a synergistic anti-tumor effect of the combination of DTX and PIC.

Co-Delivery P-Gp Inhibitors

P-glycoprotein (P-gp), the first efflux protein found to be overexpressed in breast cancer cells, is considered to be a key player in the efflux of chemotherapeutic drugs, and strategies to block or bypass the efflux function of a drug using P-gp inhibitors are highly recommended in cancer therapy.[173] Tariquidar (TRQ) is a third-generation P-gp inhibitor, and co-administration of P-gp inhibitors and DTX has been extensively studied to improve outcomes in multidrug-resistant cancers.[174] Chang et al[175] developed a novel drug nanocarrier (PRN) for co-loading the chemotherapeutic drugs DTX and TRQ. All DTX-loaded formulations or combination treatments exhibited concentration-dependent cytotoxicity in MCF-7 and MCF-7/ADR BC cells. DˆT-PRN exhibited the highest MDR reversal efficiency in MCF7/ADR cells, increasing cytotoxicity and apoptosis. In the MCF7/ADR hormonal nude mouse model, the DˆT-PRN treatment group showed higher anti-tumor effects compared to the D-PRN and D+T-PRN groups. In addition, DˆT-PRN significantly increased the apoptosis rate, which was superior to that of monotherapy. However, this study lacks an assessment of systemic toxicity, pharmacokinetics, and long-term efficacy. Furthermore, the drug release rate does not entirely correlate with the synergistic rate, and its potential for clinical application requires further validation.

Co-Delivery Antibiotic

Salinomycin (SAL) is a monocarboxypolyether antibiotic derived from Streptomyces albicans.[176] It can precisely kill cancer stem cells (CSCs), especially BCSCs, through a variety of mechanisms, including inhibiting cell proliferation, invasion and migration, modulating cell death, and reversing the immunosuppressive microenvironment, thereby preventing tumor growth and metastasis.[177] It has been demonstrated that the combination of salinomycin with PTX or DTX increases apoptosis in BC cell lines that are insufficiently sensitive to salinomycin.[178] Gao et al[152] developed a PLGA/TPGS nanoparticle, namely NSD, which was designed for the co-delivery of DTX and SAL. SAL/DTX molar ratio of 1:1 exhibited a synergistic impact on MCF-7 cells and MCF-7-MS cells. In the case of MCF-7 cells, the IC_{50} value of NSD was notably lower than those of NS and ND. Compared to the combination of two separate nanoparticles

(NS and ND), the co-delivered nanoparticles (NSD) demonstrated greater cytotoxicity to MCF-7 cells. For MCF-7 cells, the combination therapy proved to be more effective than monotherapy, and among them, NSD showed the most potent anti-tumor effect against MCF-7 cells.

Conclusions and Perspective

BC is the most malignant and aggressive tumor in women and its incidence is gradually increasing. Although the treatment modalities for BC include surgery, chemotherapy and radiotherapy, it has no absolute cure and remains a life-threatening disease for human beings.[179,180] DTX, a PTX-based drug, is used as one of the most effective chemotherapeutic agents for the treatment of breast cancer, and is also widely used in head and neck, gastric, prostate, and non-small cell lung cancers.[181] The poor water solubility, low bioavailability and high toxicity of DTX greatly limit its clinical application. The rise of nanotechnology has brought new opportunities for the development of DTX drug delivery systems. Nanomaterials possess unique size characteristics that improve drug solubility, allow passive targeting through the EPR effect, also control drug release, and can be further modified for long in vivo circulation, RES clearance, and tumor-specific targeting.[182] The advancement of nanomedicines necessitates sustained clinical translation and commercialisation efforts. However, the majority of nanomedicine products fail to achieve high efficacy or therapeutic enhancement and/or safety assurance, exhibiting limited targeting efficacy, thereby hindering successful clinical translation and commercialisation. In most instances of failed translation, nanomedicines demonstrating exceptional efficacy in animal models often struggle to fulfil anticipated prospects in clinical trials. This paper reviews the DTX targeted drug delivery system and the challenges confronting its clinical translation.

In recent years, with the deepening penetration of nanotechnology into the biomedical field, numerous nanomedicines for anticancer drugs have progressed from the laboratory to clinical settings. Significant breakthroughs have also been achieved in the research of DTX nanomedicines. The latest findings indicate that DTX nanomedicines demonstrate considerable advantages in pharmacokinetics, pharmacodynamics, and toxicity, and have already made progress in both clinical applications and research. For instance, DoceAqualip® is a nanosome lipid suspension that has demonstrated efficacy and safety in the treatment of locally advanced or metastatic breast cancer.[183] In addition, DoceAqualip® is being prospectively evaluated in patients with triple negative breast cancer (NCT03671044).[184] CLEOPATRA Phase III Trial Establishes Combination of Patuzumab, Trastuzumab and DTX as Standard First-Line Treatment for HER2-Positive Locally Recurrent/Metastatic Breast Cancer.[185] A Phase III registry clinical study (NCT05838066) of HER2 bispecific antibody (KN026) in combination with albumin-conjugated DTX (HB1801) for the treatment of first-line HER2-positive breast cancer is ongoing. The combination therapy has demonstrated good tolerability and significant clinical benefit in previous Phase II clinical studies (KN026-201, NCT04165993). DTX combined with adriamycin and cyclophosphamide for postoperative adjuvant chemotherapy in patients with lymph node-positive breast cancer. However, the application of DTX nanomedicines still faces multiple challenges: firstly, passive targeting efficacy is limited, requiring strict control of nanoparticle size and surface properties to evade recognition by the kidneys and reticuloendothelial system (RES). Nanodrugs are relatively unstable due to their complex nature, prone to aggregation, precipitation, disintegration, and degradation, which further diminishes passive targeting efficacy. Secondly, clinical success cases of nanoparticle drugs based on the EPR effect remain limited and inconclusive. Although thoroughly validated in animal models, no model can perfectly replicate human tumor pathology. Differences between mouse models and human cancers in vascular permeability and tumor stroma mean nanoparticle drugs highly accumulate in mouse xenograft tumors, yet this effect is unstable in human cancers. The dense extracellular matrix within tumor tissue further impedes drug penetration. Therefore, improving nanoparticle biodistribution, accumulation, and stability through appropriate in vivo testing is essential.[186] Should animal models fully replicate the histological features and heterogeneity of human cancers, clinical translation of anticancer nanomedicines may achieve significant breakthroughs. Thirdly, safety and evaluation issues are prominent. Safe and effective carriers are key to the clinical translation of DTX biologics.[187] Although nanoplatforms markedly alter drug biodistribution within the body, compared to free molecule delivery, their formulations are more prone to accumulation in normal organs such as the liver, lungs, and spleen. Safety concerns arising from this biodistribution must be addressed, while the biocompatibility and biodegradability of nanoparticles warrant particular

scrutiny. Current safety assessment methods resemble those for conventional drugs, necessitating the development of novel nanotoxicity detection approaches and the implementation of long-term toxicity testing.[134,188]

To overcome the challenges in the clinical application of DTX nanomedicines, researchers have turned their attention to active targeting technologies. By modifying specific ligands on the surface of nanoparticles, such as targeting small molecules, peptides, monoclonal antibodies, etc, the endocytosis of drugs is mediated by molecules such as antibodies and ligands that can specifically recognise and interact with cancer cells, thus realising the active targeting of DTX nano-delivery system in the body. Ligand-mediated targeting strategies can reduce nanoparticle toxicity by enhancing drug concentration within tumors while minimising distribution to vital organs. Although this increases nanoparticle complexity, it circumvents the aforementioned nanotoxicity challenges. Furthermore, before nanoparticles reach tumor sites and exert their surface ligand-targeted functions, they must traverse multiple biological barriers and harness beneficial EPR effect. Numerous studies confirm that the EPR effect forms the foundation for achieving active targeted delivery. Although actively targeted nanosystems have been extensively explored in research, only a few have reached the clinical trial stage. Most of the nanosystems currently approved for clinical us e cannot be actively targeted, but rely on passive targeting for their efficacy,[189] and actively targeted nanosystems still face many challenges during clinical translation. Selection of appropriate targeting molecules is the key to active targeting technology, but tumor cell surface markers are not only complex and diverse, but also have individual differences. It is a challenge to select targeting molecules with high specificity and affinity and to optimise them. Furthermore, the non-uniform expression of membrane receptors hinders active targeting from attaining the expected outcome. Ligand binding does not always confer advantages. For instance, when the specific ligand modified on the nanocarrier has an overly high affinity for the tumor cell receptor, it may trigger a "binding site barrier". As a result, this barrier impedes the efficient penetration of the nanomedicine into the tumor tissue. Although active targeting demonstrates significant advantages in vitro, in vivo active targeting methods remain relatively ineffective and may only be relevant in a limited number of circumstances, such as the treatment of haematological malignancies. In serum environments, nanoparticle surfaces readily adsorb plasma proteins to form protein coats. This phenomenon may obscure targeting moieties and diminish ligand binding capacity (with targeting efficacy declining as serum concentrations increase), while also altering the physicochemical properties of nanoparticles and reducing the accessibility of targeting ligands. Overcoming protein coat shielding, maintaining ligand bioactivity, and achieving optimal spatial orientation remain critical unresolved challenges.[188,190] Therefore, it is important to use genomics, proteomics and other high-tech means to explore more targets with high specificity, high effectiveness and significant expression differences between tumor cells and normal cells, and to develop new biocompatible, biodegradable carrier materials with intelligent response properties, so as to accelerate the transformation of active targeted drug delivery system for BC from clinical trials to clinical applications.

Physicochemical nanomedicine complexes show great potential for application in targeted BC therapy, which utilise physicochemical to enhance drug sensitivity. According to the characteristics of the TME, such as changes in pH, temperature and enzymes, the precise release of drugs is achieved. For example, under the action of tumor acidic microenvironment, the structure of nanoparticles changes, which results in the release of DTX, increasing the effective concentration of the drug at the tumor site and reducing the damage to normal tissues.[191] However, relatively few such delivery systems have actually entered clinical trials. This is principally attributed to the complexity of the organism, the heterogeneity of tumors-encompassing the specificity of receptor expression and the efficacy of the TME stimulus response and the unfavourable prognosis of breast cancer, like drug resistance, metastasis, and recurrence. The preparation process is often intricate, yielding favourable results in small-batch laboratory production but proving challenging to maintain consistent quality during large-scale manufacturing. Characterising product interactions with biological systems through in vitro and in vivo assessments. Whilst in vivo trials furnish crucial efficacy and toxicity data, they entail substantial costs. In vitro alternatives, though valuable, struggle to replicate the in vivo environment due to the complexity of human organs, tissues, and diseases. Traditional in vitro cell culture models lack the complexity of biological tissues and cannot control fluid flow. These factors necessitate overcoming numerous technical and safety-related hurdles during the translation from laboratory research to clinical application. Consequently, developing smarter delivery systems requires a profound understanding of the physiological underpinnings of both healthy and diseased tissues. Advancements in animal models capable of simulating human heterogeneity and anatomical histological features,

or the construction of microfluidic devices that mimic physiological flow while capturing nanoparticle-cell interactions, will significantly enhance the translational efficacy of nanomedicines.

Although DTX demonstrates significant efficacy in cancer treatment, monotherapy has failed to meet clinical requirements in long-term management. Recently, efforts have focused on combining DTX with other therapeutic strategies, yielding encouraging results in cancer treatment.[192] Nanoplatform-based DTX co-delivery therapy strategies, such as combining with active ingredients of TCM, photothermal therapy and gene therapy, have not only improved the pharmacokinetic properties of the drugs by precisely targeting the tumor cells, but also achieved remarkable results in overcoming MDR. Several clinical trials have confirmed the effectiveness and safety of this co-delivery system. Therefore, the DTX-based co-administration system is expected to achieve clinical translation. Of course, co-administration systems face some limitations. For example, differences in pharmacological fate and pharmacokinetic profiles of individual therapeutic agents may lead to severe side effects and systemic toxicity. In addition to adjusting the doses and ratios of therapeutic agents, the design of co-delivery systems is extremely challenging; for example, determining the location of drug release, the sequence of administration, and the rate of release of the two therapeutic agents, which are critical for therapeutic efficacy. Although a variety of co-delivery systems have been designed in preclinical studies in recent years, few exist on the market.[193] The use of combination therapy also requires consideration of controlling the dose of combination therapy and avoiding the side effects of such co-delivery systems. Only by overcoming these difficulties can we further promote the clinical translation process of DTX-based co-delivery systems and bring more practical and effective treatment options for breast cancer patients. Preclinical data, particularly regarding immunotoxicity, cannot accurately predict the safety of nanomedicines, and the data obtained cannot always be extrapolated to humans.

In summary, nano-drug delivery systems have great potential for DTX delivery and good prospects for the treatment of breast cancer. At present, merely a small number of nanosystems have received approval from the FDA. A considerable number of nanomedicines are still in the clinical trial phase. Evidently, there remains a substantial distance to cover before their successful translation into actual clinical applications. The development of nanomaterials is rapid and diverse and can address many insurmountable clinical problems. However, it must also be acknowledged that there are still some limitations for application in breast cancer. Despite numerous studies having shown the biocompatibility and safety of various nanomaterials, the potential toxicity associated with them still cannot be predicted with certainty.[194] Previous studies have documented adverse immune responses following nanomedicine administration, including allergic or hypersensitivity reactions. Consequently, to achieve one of nanomedicine's core objectives—minimising adverse side effects—it is imperative to fully consider drug-immune system interactions. The primary challenge currently lies in the stark discrepancy between the promising performance of numerous nanomedicines in laboratory-based in vitro and in vivo preclinical studies, and their outcomes in clinical trials. Despite the availability of diverse animal models-ranging from subcutaneous/in situ xenograft models derived from cell lines (such as 4T1 or MCF-7) - there remains a lack of tumor models capable of comprehensively reproducing all characteristics of human cancers. Consequently, developing novel animal models that simulate human tumor heterogeneity and specific physiological features could significantly enhance the translational efficiency of therapeutic nanosystems.[195] With a deeper understanding of the opportunities and challenges facing nanotechnology, smarter, safer, quality-controlled and easily scaled-up production of nano-delivery systems will provide new solutions to achieve therapeutic treatments for BC.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca a Cancer J Clinicians*. 2024;74:229–263. doi:10.3322/caac.21834
2. Katsura C, Ogunmwonyi I, Kankam HK, Saha S. Breast cancer: presentation, investigation and management. *Br J Hosp Med*. 2022;83:1–7. doi:10.12968/hmed.2021.0459
3. Rossi L, Mazzara C, Pagani O. Diagnosis and Treatment of Breast Cancer in Young Women. *Curr Treat Option Oncol*. 2019;20:86. doi:10.1007/s11864-019-0685-7
4. Yan J, Liu Z, Du S, et al. Diagnosis and treatment of breast cancer in the precision medicine era. *Methods Mol Biol*. 2020;2204:53–61. doi:10.1007/978-1-0716-0904-0_5
5. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J clin oncol*. 2008;26:1275–1281. doi:10.1200/jco.2007.14.4147
6. Barzaman K, Karami J, Zarei Z, et al. Breast cancer: biology, biomarkers, and treatments. *Int Immunopharmacol*. 2020;84:106535. doi:10.1016/j.intimp.2020.106535
7. Singletary SE. Minimally invasive techniques in breast cancer treatment. *Semin Surg Oncol*. 2001;20:246–250. doi:10.1002/ssu.1040
8. Gozzo Tde O, de Souza SG, Moysés AM, Panobianco MS, de Almeida AM. Incidence and management of chemotherapy-induced nausea and vomiting in women with breast cancer. *Rev Gaucha Enferm*. 2014;35:117–123. doi:10.1590/1983-1447.2014.03.42068
9. Cánovas B, Igea A, Sartori AA, et al. Targeting p38α increases DNA damage, chromosome instability, and the anti-tumoral response to taxanes in breast cancer cells. *Cancer Cell*. 2018;33(6):1094–1110.e1098. doi:10.1016/j.ccell.2018.04.010
10. Shi C, Zhang Z, Shi J, Wang F, Luan Y. Co-delivery of docetaxel and chloroquine via PEO-PPO-PCL/TPGS micelles for overcoming multidrug resistance. *Int J Pharm*. 2015;495:932–939. doi:10.1016/j.ijpharm.2015.10.009
11. de Weger VA, Beijnen JH, Schellens JH. Cellular and clinical pharmacology of the taxanes docetaxel and paclitaxel--a review. *Anti-Cancer Drugs*. 2014;25:488–494. doi:10.1097/cad.0000000000000093
12. Wen G, Qu -X-X, Wang D, et al. Recent advances in design, synthesis and bioactivity of paclitaxel-mimics. *Fitoterapia*. 2016;110:26–37. doi:10.1016/j.fitote.2016.02.010
13. Feng L, Qi S, Lin M. Efficacy and survival rate of intensity-modulated radiotherapy combined with chemotherapy for elderly patients with locally advanced oropharyngeal cancer. *Exp Ther Med*. 2018;15:2475–2479. doi:10.3892/etm.2017.5682
14. Xu L, Ye JM, Zhu SN, et al. [Analysis of neoadjuvant docetaxel, carboplatin and trastuzumab (TCH) in HER-2-positive breast cancer]. *Zhonghua Yi Xue Za Zhi*. 2018;98:907–911. doi:10.3760/cma.j.issn.0376-2491.2018.12.006 Danish
15. Rafiei P, Haddadi A. Docetaxel-loaded PLGA and PLGA-PEG nanoparticles for intravenous application: pharmacokinetics and biodistribution profile. *Int J Nanomed*. 2017;12:935–947. doi:10.2147/ijn.S121881
16. Jain S, Spandana G, Agrawal AK, Kushwah V, Thanki K. Enhanced antitumor efficacy and reduced toxicity of docetaxel loaded estradiol functionalized stealth polymeric nanoparticles. *Mol Pharm*. 2015;12:3871–3884. doi:10.1021/acs.molpharmaceut.5b00281
17. ten Tije AJ, Verweij J, Loos WJ, Sparreboom A. Pharmacological effects of formulation vehicles: implications for cancer chemotherapy. *Clin Pharmacokinet*. 2003;42:665–685. doi:10.2165/00003088-200342070-00005
18. Logie J, Ganesh AN, Aman AM, Al-Awar RS, Shoichet MS. Preclinical evaluation of taxane-binding peptide-modified polymeric micelles loaded with docetaxel in an orthotopic breast cancer mouse model. *Biomaterials*. 2017;123:39–47. doi:10.1016/j.biomaterials.2017.01.026
19. McKeage K. Nanosomal docetaxel lipid suspension: a guide to its use in cancer. *Clin Drug Invest*. 2017;37:405–410. doi:10.1007/s40261-017-0510-7
20. Overchuk M, Zheng G. Overcoming obstacles in the tumor microenvironment: recent advancements in nanoparticle delivery for cancer theranostics. *Biomaterials*. 2018;156:217–237. doi:10.1016/j.biomaterials.2017.10.024
21. Ernsting MJ, Murakami M, Roy A, Li S-D. Factors controlling the pharmacokinetics, biodistribution and intratumoral penetration of nanoparticles. *J Control Release*. 2013;172:782–794. doi:10.1016/j.jconrel.2013.09.013
22. Wang S, Yu G, Wang Z, et al. Hierarchical tumor microenvironment-responsive nanomedicine for programmed delivery of chemotherapeutics. *Adv Mater*. 2018;30:e1803926. doi:10.1002/adma.201803926
23. Kafle U, Agrawal S, Dash AK. Injectable nano drug delivery systems for the treatment of breast cancer. *Pharmaceutics*. 2022;14:2783. doi:10.3390/pharmaceutics14122783
24. Sakhrani NM, Padh H. Organelle targeting: third level of drug targeting. *Drug Des Devel Ther*. 2013;7:585–599. doi:10.2147/dddt.S45614
25. Biswas S, Kumari P, Lakhani PM, Ghosh B. Recent advances in polymeric micelles for anti-cancer drug delivery. *Eur J Pharm Sci*. 2016;83:184–202. doi:10.1016/j.ejps.2015.12.031
26. Agrahari V, Agrahari V. Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities. *Drug Discovery Today*. 2018;23:974–991. doi:10.1016/j.drudis.2018.01.047
27. Tian H, Zhao F, Qi Q-R, Yue B-S, Zhai B-T. Targeted drug delivery systems for elemene in cancer therapy: the story thus far. *Biomed Pharmacother*. 2023;166:115331. doi:10.1016/j.biopha.2023.115331
28. Chenthamara D, Subramaniam S, Ramakrishnan SG, et al. Therapeutic efficacy of nanoparticles and routes of administration. *Biomater Res*. 2019;23:20. doi:10.1186/s40824-019-0166-x
29. Herrmann I, Li ZA, Bahal R, Conde J. Translating nanomedicines from the lab to the clinic. *Cell Rep Phy Sci*. 2025;6:102357. doi:10.1016/j.xcrp.2024.102357
30. Alqaraghuli HGJ, Kashanian S, Rafipour R. A review on targeting nanoparticles for breast cancer. *Current Pharm Biotechnol*. 2019;20:1087–1107. doi:10.2174/1389201020666190731130001
31. Alshamrani M, Ayon NJ, Alsalhi A, Akinjole O. Self-assembled nanomicellar formulation of docetaxel as a potential breast cancer chemotherapeutic system. *Life*. 2022;12:485. doi:10.3390/life12040485

32. Lu X, Fang M, Yang Y, et al. PEG-conjugated triacontanol micelles as docetaxel delivery systems for enhanced anti-cancer efficacy. *Drug Deliv Transl Res*. 2020;10:122–135. doi:10.1007/s13346-019-00667-6
33. Sreekanth V, Pal S, Kumar S, et al. Self-assembled supramolecular nanomicelles from a bile acid-docetaxel conjugate are highly tolerable with improved therapeutic efficacy. *Biomater Sci*. 2021;9:5626–5639. doi:10.1039/d1bm00031d
34. Jain S, Desai MR, Nallamothu B, et al. Partial inclusion complex assisted crosslinked β-cyclodextrin nanoparticles for improving therapeutic potential of docetaxel against breast cancer. *Drug Delivery Transl Res*. 2021;12:562–576. doi:10.1007/s13346-021-00956-z
35. Wang Y, Zuo A, Huang X, et al. Docetaxel-loaded PAMAM-based poly (γ-benzyl-l-glutamate)-b-d-α-tocopheryl polyethylene glycol 1000 succinate nanoparticles in human breast cancer and human cervical cancer therapy. *J Microencapsul*. 2019;36:552–565. doi:10.1080/02652048.2019.1654002
36. Miraj S, Saeed H, Iqtedar M, et al. Docetaxel-loaded methoxy poly(ethylene glycol)-poly (l-lactic acid) nanoparticles for breast cancer: synthesis, characterization, method validation, and cytotoxicity. *Pharmaceuticals*. 2023. 16. doi:10.3390/ph16111600
37. Lai YH, Chiang CS, Hsu CH, Cheng HW, Chen SY. Development and characterization of a fucoidan-based drug delivery system by using hydrophilic anticancer polysaccharides to simultaneously deliver hydrophobic anticancer drugs. *Biomolecules*. 2020;10:970. doi:10.3390/biom10070970
38. Ha-Lien Tran P, Wang T, Yang C, Tran TTD, Duan W. Development of conjugate-by-conjugate structured nanoparticles for oral delivery of docetaxel. *Mater Sci Eng C Mater Biol Appl*. 2020;107:110346. doi:10.1016/j.msec.2019.110346
39. Dong P, Liu J, Lv H, et al. The enhanced antitumor activity of the polymeric conjugate covalently coupled with docetaxel and docosahexaenoic acid. *Biomater Sci*. 2022;10:3454–3465. doi:10.1039/d2bm00337f
40. Otaka A, Yamaguchi T, Saisho R, Hiraga T, Iwasaki Y. Bone-targeting phospholipid polymers to solubilize the lipophilic anticancer drug. *J Biomed Mater Res Part A*. 2020;108:2090–2099. doi:10.1002/jbm.a.36968
41. Jadon RS, Sharma M. Docetaxel-loaded lipid-polymer hybrid nanoparticles for breast cancer therapeutics. *J Drug Delivery Sci Technol*. 2019;51:475–484. doi:10.1016/j.jddst.2019.03.039
42. Zawilska P, Machowska M, Wisniewski K, et al. Novel pegylated liposomal formulation of docetaxel with 3-n-pentadecylphenol derivative for cancer therapy. *Eur J Pharm Sci*. 2021;163:105838. doi:10.1016/j.ejps.2021.105838
43. Li N, Fu T, Fei W, et al. Vitamin E D-alpha-tocopheryl polyethylene glycol 1000 succinate-conjugated liposomal docetaxel reverses multidrug resistance in breast cancer cells. *J Pharm Pharmacol*. 2019;71:1243–1254. doi:10.1111/jphp.13126
44. Vakili-Ghartavol R, Rezayat SM, Faridi-Majidi R, Sadri K, Jaafari MR. Optimization of docetaxel loading conditions in liposomes: proposing potential products for metastatic breast carcinoma chemotherapy. *Sci Rep*. 2020;10. doi:10.1038/s41598-020-62501-1
45. da Rocha MCO, da Silva PB, Radicchi MA, et al. Docetaxel-loaded solid lipid nanoparticles prevent tumor growth and lung metastasis of 4T1 murine mammary carcinoma cells. *J Nanobiotechnology*. 2020;18:43. doi:10.1186/s12951-020-00604-7
46. Rai N, Madni A, Faisal A, et al. Glyceryl monostearate based solid lipid nanoparticles for controlled delivery of docetaxel. *Curr drug deliv*. 2021;18:1368–1376. doi:10.2174/1567201818666210203180153
47. Carvalho FV, Ribeiro LNDM, Moura LDD, et al. Docetaxel loaded in copaiba oil-nanostructured lipid carriers as a promising DDS for breast cancer treatment. *Molecules*. 2022;27:8838. doi:10.3390/molecules27248838
48. Al Saqr A, Wani SUD, Gangadharappa HV, et al. Enhanced cytotoxic activity of docetaxel-loaded silk fibroin nanoparticles against breast cancer cells. *Polymers*. 2021;13:1416. doi:10.3390/polym13091416
49. Gong M, Zhang Q, Zhao Q, et al. Development of synthetic high-density lipoprotein-based ApoA-I mimetic peptide-loaded docetaxel as a drug delivery nanocarrier for breast cancer chemotherapy. *Drug Deliv*. 2019;26:708–716. doi:10.1080/10717544.2019.1618420
50. Bathara M, Date T, Chaudhari D, et al. Exploring the promising potential of high permeation vesicle-mediated localized transdermal delivery of docetaxel in breast cancer to overcome the limitations of systemic chemotherapy. *Mol Pharm*. 2020;17:2473–2486. doi:10.1021/acs.molpharmaceut.0c00211
51. Ajdari M, Ranjbar A, Karimian K, et al. Characterization and evaluation of nano-niosomes encapsulating docetaxel against human breast, pancreatic, and pulmonary adenocarcinoma cancer cell lines. *J Biomed Phy Eng*. 2024;14:159–168. doi:10.31661/jbpe.v0i0.2401-1708
52. Thotakura N, Sharma S, Khurana RK, et al. Aspartic acid tagged carbon nanotubols as a tool to deliver docetaxel to breast cancer cells: reduced hemotoxicity with improved cytotoxicity. *Toxicol in vitro*. 2019;59:126–134. doi:10.1016/j.tiv.2019.04.012
53. Pham DT, Chokamonsirikun A, Phattaravorakarn V, Tiyaboonchai W. Polymeric micelles for pulmonary drug delivery: a comprehensive review. *J Mater Sci*. 2020;56:2016–2036. doi:10.1007/s10853-020-05361-4
54. Ahlawat J, Henriquez G, Narayan M. Enhancing the delivery of chemotherapeutics: role of biodegradable polymeric nanoparticles. *Molecules*. 2018;23:2157. doi:10.3390/molecules23092157
55. Floyd TG, Gurnani P, Rho JY. Characterisation of polymeric nanoparticles for drug delivery. *Nanoscale*. 2025;17:7738–7752. doi:10.1039/d5nr00071h
56. Garg NK, Tandel N, Jadon RS, Tyagi RK, Katare OP. Lipid-polymer hybrid nanocarrier-mediated cancer therapeutics: current status and future directions. *Drug Discovery Today*. 2018;23:1610–1621. doi:10.1016/j.drudis.2018.05.033
57. Bose RJC, Ravikumar R, Karuppagounder V, et al. Lipid-polymer hybrid nanoparticle-mediated therapeutics delivery: advances and challenges. *Drug Discovery Today*. 2017;22:1258–1265. doi:10.1016/j.drudis.2017.05.015
58. Daeihamed M, Dadashzadeh S, Haeri A, Akhlaghi MF. Potential of liposomes for enhancement of oral drug absorption. *Curr drug deliv*. 2017;14:289–303. doi:10.2174/1567201813666160115125756
59. Qushawy M, Nasr ALI. Solid lipid nanoparticles (SLNs) as nano drug delivery carriers: preparation, characterization and application. *Int J Appl Pharm*. 2019;1–9. doi:10.22159/ijap.2020v12i1.35312
60. Sandri G, Motta S, Bonferoni MC, et al. Chitosan-coupled solid lipid nanoparticles: tuning nanostructure and mucoadhesion. *Eur J Pharm Biopharm*. 2017;110:13–18. doi:10.1016/j.ejpb.2016.10.010
61. Salvi VR, Pawar P. Nanostructured lipid carriers (NLC) system: a novel drug targeting carrier. *J Drug Delivery Sci Technol*. 2019;51:255–267. doi:10.1016/j.jddst.2019.02.017
62. Kim CH, Lee SG, Kang MJ, Lee S, Choi YW. Surface modification of lipid-based nanocarriers for cancer cell-specific drug targeting. *J Pharm Invest*. 2017;47:203–227. doi:10.1007/s40005-017-0329-5
63. Kaltbeitzel J, Wich PR. Protein-based nanoparticles: from drug delivery to imaging, nanocatalysis and protein therapy. *Angew Chem*. 2023;62:e202216097. doi:10.1002/anie.202216097

64. DeFrates K, Markiewicz T, Gallo P, et al. Protein polymer-based nanoparticles: fabrication and medical applications. *Int J Mol Sci*. 2018;19:1717. doi:10.3390/ijms19061717
65. Jain S, Khare P, Date T, et al. Mechanistic insights into high permeation vesicle-mediated synergistic enhancement of transdermal drug permeation. *Nanomedicine*. 2019;14:2227–2241. doi:10.2217/nnm-2018-0519
66. Son KH, Hong JH, Lee JW. Carbon nanotubes as cancer therapeutic carriers and mediators. *Int J Nanomed*. 2016;11:5163–5185. doi:10.2147/ijn.S112660
67. Mohanraj V, Chen Y. Nanoparticles - a review. *%J Trop J Pharm Res*. 2006;05:561–573.
68. Dai L, Liu J, Luo Z, Li M, Cai K. Tumor therapy: targeted drug delivery systems. *J Mat Chem B*. 2016;4:6758–6772. doi:10.1039/c6tb01743f
69. Varshosaz J, Hassanzadeh F, Hashemi-Beni B, Minaiyan M, Enteshari S. Tissue distribution and systemic toxicity evaluation of raloxifene targeted polymeric micelles of poly (styrene-maleic acid)-poly (amide- ether-ester-imide)-poly (ethylene glycol) loaded with docetaxel in breast cancer bearing mice. *Recent Patents Anti-Cancer Drug Disc*. 2019;14:280–291. doi:10.2174/1574892814666190919163731
70. Tran NP, Tran P, Yoo S-Y, et al. Sialic acid-decorated liposomes enhance the anti-cancer efficacy of docetaxel in tumor-associated macrophages. *Biomater Adv*. 2023;154:213606. doi:10.1016/j.bioadv.2023.213606
71. Song C, Gao C, Zhao J, Wang Z. Construction of long-circulation EpCAM targeted drug delivery system and its application in the diagnosis and treatment of breast cancer. *J Biomater Applications*. 2020;35:947–957. doi:10.1177/0885328220965135
72. Andisheh F, Oroojalian F, Shakour N, et al. Docetaxel encapsulation in nanoscale assembly micelles of folate-PEG-docetaxel conjugates for targeted fighting against metastatic breast cancer in vitro and in vivo. *Int J Pharm*. 2021;605:120822. doi:10.1016/j.ijpharm.2021.120822
73. Kazemi M, Emami J, Hasanzadeh F, et al. In vitro and in vivo evaluation of novel DTX-loaded multifunctional heparin-based polymeric micelles targeting folate receptors and endosomes. *Recent Pat Anticancer Drug Discov*. 2020;15:341–359. doi:10.2174/1574892815666201006124604
74. Sharma S, Pukale SS, Sahel DK, et al. Folate-targeted cholesterol-grafted lipo-polymeric nanoparticles for chemotherapeutic agent delivery. *AAPS Pharm Sci Tech*. 2020;21:280. doi:10.1208/s12249-020-01812-y
75. Zhang H, Dong S, Zhang S, et al. pH-responsive lipid polymer hybrid nanoparticles (LPHNs) based on poly (β-amino ester) as a promising candidate to resist breast cancers. *J Drug Delivery Sci Technol*. 2021;61:102102. doi:10.1016/j.jddst.2020.102102
76. Sui F, Fang Z, Li L, et al. pH-triggered "PEG" sheddable and folic acid-targeted nanoparticles for docetaxel delivery in breast cancer treatment. *Int J Pharm*. 2023;644:123293. doi:10.1016/j.ijpharm.2023.123293
77. Ghassami E, Varshosaz J, Mirian M, Jahanian-Najafabadi A. HER-2 aptamer-targeted Ecoflex(®) nanoparticles loaded with docetaxel promote breast cancer cells apoptosis and anti-metastatic effect. *IET Nanobiotechnol*. 2019;13:428–434. doi:10.1049/iet-nbt.2018.5047
78. Conte C, Longobardi G, Barbieri A, et al. Non-covalent strategies to functionalize polymeric nanoparticles with NGR peptides for targeting breast cancer. *Int J Pharm*. 2023;633:122618. doi:10.1016/j.ijpharm.2023.122618
79. Korake S, Salve R, Gajbhiye V, Pawar A. αvβ3 integrin-targeted pH-responsive dendritic nanocarriers for enhanced anti-tumor efficacy of docetaxel against breast cancer. *J Drug Delivery Sci Technol*. 2024;99:105946. doi:10.1016/j.jddst.2024.105946
80. Di Gregorio E, Romiti C, Di Lorenzo A, et al. RGD_PLGA nanoparticles with docetaxel: a route for improving drug efficiency and reducing toxicity in breast cancer treatment. *Cancers*. 2022;15(1):8. doi:10.3390/cancers15010008
81. Li S, Qiu M, Guo J, et al. Coating-Sheddable CD44-Targeted Poly(d,l-lactide-co-glycolide) nanomedicines fabricated by using photoclick-crosslinkable surfactant. *Adv Ther*. 2019. 3. doi:10.1002/adtp.201900160
82. Fang H, Zhao X, Gu X, et al. CD44-targeted multifunctional nanomedicines based on a single-component hyaluronic acid conjugate with all-natural precursors: construction and treatment of metastatic breast tumors in vivo. *Biomacromolecules*. 2020;21(1):104–113. doi:10.1021/acs.biomac.9b01012
83. Lee J-Y, Lee HS, Kang N-W, et al. Blood component ridable and CD44 receptor targetable nanoparticles based on a maleimide-functionalized chondroitin sulfate derivative. *Carbohydr Polym*. 2020;230:115568. doi:10.1016/j.carbpol.2019.115568
84. Wang W, Zhang X, Li Z, et al. Dendronized hyaluronic acid-docetaxel conjugate as a stimuli-responsive nano-agent for breast cancer therapy. *Carbohydr Polym*. 2021;267:118160. doi:10.1016/j.carbpol.2021.118160
85. Abdelmoneem MA, Abd Elwakil MM, Khattab SN, et al. Lactoferrin-dual drug nanoconjugate: synergistic anti-tumor efficacy of docetaxel and the NF-κB inhibitor celastrol. *Mater Sci Eng C*. 2021. 118. doi:10.1016/j.msec.2020.111422
86. Xia J, Ma S, Zhu X, et al. Versatile ginsenoside Rg3 liposomes inhibit tumor metastasis by capturing circulating tumor cells and destroying metastatic niches. *Sci Adv*. 2022;8:eabj1262. doi:10.1126/sciadv.abj1262
87. Cheng SB, Graeber CT, Quinn JA, Filardo EJ. Retrograde transport of the transmembrane estrogen receptor, G-protein-coupled-receptor-30 (GPR30/GPER) from the plasma membrane towards the nucleus. *Steroids*. 2011;76:892–896. doi:10.1016/j.steroids.2011.02.018
88. Lappano R, Pisano A, Maggiolini M. GPER function in breast cancer: an overview. *Front Endocrinol*. 2014;5:66. doi:10.3389/fendo.2014.00066
89. Filardo EJ, Graeber CT, Quinn JA, et al. Distribution of GPR30, a seven membrane-spanning estrogen receptor, in primary breast cancer and its association with clinicopathologic determinants of tumor progression. *Clin Cancer Res*. 2006;12:6359–6366. doi:10.1158/1078-0432.Ccr-06-0860
90. Macauley MS, Crocker PR, Paulson JC. Siglec-mediated regulation of immune cell function in disease. *Nat Rev Immunol*. 2014;14:653–666. doi:10.1038/nri3737
91. Song Y, She Z, Huang Z, et al. Are third-generation active-targeting nanoformulations definitely the best? In vitro and in vivo comparisons of pixantrone-loaded liposomes modified with different sialic acid derivatives. *Drug Deliv Transl Res*. 2022;12:647–661. doi:10.1007/s13346-021-00973-y
92. Zhang T, Zhou S, Hu L, et al. Polysialic acid-polyethylene glycol conjugate-modified liposomes as a targeted drug delivery system for epirubicin to enhance anticancer efficiency. *Drug Deliv Transl Res*. 2018;8:602–616. doi:10.1007/s13346-018-0496-6
93. Satelli A, Brownlee Z, Mitra A, Meng QH, Li S. Circulating tumor cell enumeration with a combination of epithelial cell adhesion molecule- and cell-surface vimentin-based methods for monitoring breast cancer therapeutic response. *Clin Chem*. 2015;61:259–266. doi:10.1373/clinchem.2014.228122
94. Oh I-H, Cho KJ, Tran TH, Huh KM, Lee Y-K. Biofuntional nanoparticle formation and folate-targeted antitumor effect of heparin-retinoic acid conjugates. *Macromol Res*. 2012;20:520–527. doi:10.1007/s13233-012-0073-7
95. Krystofiak ES, Matson VZ, Steeber DA, Oliver JA, Kim D. Elimination of tumor cells using folate receptor targeting by antibody-conjugated, gold-coated magnetite nanoparticles in a murine breast cancer model. *J Nanomater*. 2012;2012. doi:10.1155/2012/431012

96. Lewis Phillips GD, Li G, Dugger DL, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Res*. 2008;68:9280–9290. doi:10.1158/0008-5472.Can-08-1776
97. Peyrin E. Nucleic acid aptamer molecular recognition principles and application in liquid chromatography and capillary electrophoresis. *J Sep Science*. 2009;32:1531–1536. doi:10.1002/jssc.200900061
98. Jensen LD, Nakamura M, Bräutigam L, et al. VEGF-B-Neuropilin-1 signaling is spatiotemporally indispensable for vascular and neuronal development in zebrafish. *Proc Natl Acad Sci USA*. 2015;112:E5944–5953. doi:10.1073/pnas.1510245112
99. Desgrosellier JS, Cheresh DA. Integrins in cancer: biological implications and therapeutic opportunities. *Nat Rev Cancer*. 2010;10(1):9–22. doi:10.1038/nrc2748
100. Seguin L, Desgrosellier JS, Weis SM, Cheresh DA. Integrins and cancer: regulators of cancer stemness, metastasis, and drug resistance. *Trends Cell Biol*. 2015;25(4):234–240. doi:10.1016/j.tcb.2014.12.006
101. Ramanujan S, Pluen A, McKee TD, et al. Diffusion and convection in collagen gels: implications for transport in the tumor interstitium. *Biophys J*. 2002;83(3):1650–1660. doi:10.1016/s0006-3495(02)73933-7
102. Wang X, Liang Y, Zhang Y, et al. Combination therapy of cRGD-DOX self-assembled nanoparticles and bevacizumab for breast cancer. *J Chin Pharm Sci*. 2019;28. doi:10.5246/jcps.2019.09.060
103. Mattheolabakis G, Milane L, Singh A, Amiji MM. Hyaluronic acid targeting of CD44 for cancer therapy: from receptor biology to nanomedicine. *J Drug Target*. 2015;23(7–8):605–618. doi:10.3109/1061186x.2015.1052072
104. Hu L, Ma H, Yang C, et al. Environmental responsive dual-drug synergistic and dual-targeted polymer micelles based on chondroitin sulfate for treatment of breast cancer. *Int J Biol Macromol*. 2025;311:144083. doi:10.1016/j.ijbiomac.2025.144083
105. Yu J, Xu J, Jiang R, et al. Versatile chondroitin sulfate-based nanoplatform for chemo-photodynamic therapy against triple-negative breast cancer. *Int J Biol Macromol*. 2024;265:130709. doi:10.1016/j.ijbiomac.2024.130709
106. Wang G, Kumar A, Ding W, et al. Intraductal administration of transferrin receptor-targeted immunotoxin clears ductal carcinoma in situ in mouse models of breast cancer-a preclinical study. *Proc Natl Acad Sci USA*. 2022;119:e2200200119. doi:10.1073/pnas.2200200119
107. AbdElhamid AS, Zayed DG, Helmy MW, et al. Lactoferrin-tagged quantum dots-based theranostic nanocapsules for combined COX-2 inhibitor/herbal therapy of breast cancer. *Nanomedicine*. 2018;13:2637–2656. doi:10.2217/nnm-2018-0196
108. Abd Elwakil MM, Mabrouk MT, Helmy MW, et al. Inhalable lactoferrin-chondroitin nanocomposites for combined delivery of doxorubicin and ellagic acid to lung carcinoma. *Nanomedicine*. 2018;13:2015–2035. doi:10.2217/nnm-2018-0039
109. Barbosa AM, Martel F. Targeting glucose transporters for breast cancer therapy: the effect of natural and synthetic compounds. *Cancers*. 2020;12:154. doi:10.3390/cancers12010154
110. Hong C, Wang D, Liang J, et al. Novel ginsenoside-based multifunctional liposomal delivery system for combination therapy of gastric cancer. *Theranostics*. 2019;9:4437–4449. doi:10.7150/thno.34953
111. Commander R, Wei C, Sharma A, et al. Subpopulation targeting of pyruvate dehydrogenase and GLUT1 decouples metabolic heterogeneity during collective cancer cell invasion. *Nat Commun*. 2020;11:1533. doi:10.1038/s41467-020-15219-7
112. Panda J, Satapathy BS, Mandal B, et al. Anticancer potential of docetaxel-loaded cobalt ferrite nanocarrier: an in vitro study on MCF-7 and MDA-MB-231 cell lines. *J Microencapsul*. 2021;38:36–46. doi:10.1080/02652048.2020.1842529
113. Panda J, Satapathy BS, Majumder S, et al. Engineered polymeric iron oxide nanoparticles as potential drug carrier for targeted delivery of docetaxel to breast cancer cells. *J Magn Magn Mater*. 2019;485:165–173. doi:10.1016/j.jmmm.2019.04.058
114. Taheri-Ledari R, Zhang W, Radmanesh M, et al. Multi-stimuli nanocomposite therapeutic: docetaxel targeted delivery and synergies in treatment of human breast cancer tumor. *Small*. 2020;16:e2002733. doi:10.1002/smll.202002733
115. Ghasemi S, Ahmadi L, Farjadian F. Thermo-responsive PNIPAAm-b-PLA amphiphilic block copolymer micelle as nanoplatform for docetaxel drug release. *J Mater Sci*. 2022;57:17433–17447. doi:10.1007/s10853-022-07711-w
116. Jadon RS, Sharma G, Garg NK, et al. Efficient in vitro and in vivo docetaxel delivery mediated by pH-sensitive LPHNPs for effective breast cancer therapy. *Colloids Surf B*. 2021;203:111760. doi:10.1016/j.colsurfb.2021.111760
117. Swetha KL, Paul M, Maravajjala KS, et al. Overcoming drug resistance with a docetaxel and disulfiram loaded pH-sensitive nanoparticle. *J Control Release*. 2023;356:93–114. doi:10.1016/j.jconrel.2023.02.023
118. Liu Y, Lang T, Zheng Z, et al. In vivo environment-adaptive nanocomplex with tumor cell-specific cytotoxicity enhances T cells infiltration and improves cancer therapy. *Small*. 2019;15:e1902822. doi:10.1002/smll.201902822
119. Emami J, Kazemi M, Hasanzadeh F, et al. Novel pH-triggered biocompatible polymeric micelles based on heparin-α-tocopherol conjugate for intracellular delivery of docetaxel in breast cancer. *Pharm Dev Technol*. 2020;25:492–509. doi:10.1080/10837450.2019.1711395
120. Yao P, Wang X, Wang Q, et al. Cyclic RGD-functionalized pH/ROS dual-responsive nanoparticle for targeted breast cancer therapy. *Pharmaceutics*. 2023;15:1827. doi:10.3390/pharmaceutics15071827
121. Altinbasak I, Kocak S, Sanyal R, Sanyal A. Redox-responsive nanogels for drug-delivery: thiol–maleimide and thiol–disulfide exchange chemistry as orthogonal tools for fabrication and degradation. *Polym Chem*. 2023;14:3897–3905. doi:10.1039/d3py00210a
122. Zhang R, Nie T, Wang L, et al. Facile synthesis of poly(disulfide)s through one-step oxidation polymerization for redox-responsive drug delivery. *Biomater Sci*. 2023;11:4254–4264. doi:10.1039/d3bm00461a
123. Shi Y, Li C, Yang M, Pan X, Hu J. Docetaxel-loaded redox-sensitive nanoparticles self-assembling from poly(caprolactone) conjugates with disulfide-linked poly(ethylene glycol). *J biomater sci Poly ed*. 2022;33:2185–2201. doi:10.1080/09205063.2022.2099664
124. Badparvar F, Marjani AP, Salehi R, Ramezani F. Dual pH/redox-responsive hyperbranched polymeric nanocarriers with TME-trigger size shrinkage and charge reversible ability for amplified chemotherapy of breast cancer. *Sci Rep*. 2024;14:8567. doi:10.1038/s41598-024-57296-4
125. Taghipour YD, Zarebkohan A, Salehi R, et al. Enhanced docetaxel therapeutic effect using dual targeted SRL-2 and TA1 aptamer conjugated micelles in inhibition Balb/c mice breast cancer model. *Sci Rep*. 2024. 14. doi:10.1038/s41598-024-75042-8
126. Farzin A, Etesami SA, Quint J, Memic A, Tamayol A. Magnetic nanoparticles in cancer therapy and diagnosis. *Adv Healthc Mater*. 2020;9:e1901058. doi:10.1002/adhm.201901058
127. Kyeong S, Kim J, Chang H, et al. Magnetic nanoparticles. *Adv Exp Med Biol*. 2021:191–215. doi:10.1007/978-981-33-6158-4_8
128. Rezaei B, Yari P, Sanders SM, et al. Magnetic nanoparticles: a review on synthesis, characterization, functionalization, and biomedical applications. *Small*. 2024;20:e2304848. doi:10.1002/smll.202304848

129. Cao M, Wang Y, Hu X, et al. Reversible thermoresponsive peptide-PNIPAM hydrogels for controlled drug delivery. *Biomacromolecules*. 2019;20:3601–3610. doi:10.1021/acs.biomac.9b01009
130. Huang N, Wang J, Cheng X, Xu Y, Li W. Fabrication of PNIPAM-chitosan/decatungstoeuropate/silica nanocomposite for thermo/pH dual-stimuli-responsive and luminescent drug delivery system. *J Inorg Biochem*. 2020;211:111216. doi:10.1016/j.jinorgbio.2020.111216
131. Nakayama M, Okano T, Miyazaki T, et al. Molecular design of biodegradable polymeric micelles for temperature-responsive drug release. *J Control Release*. 2006;115:46–56. doi:10.1016/j.jconrel.2006.07.007
132. Yang M, Ding Y, Zhang L, et al. Novel thermosensitive polymeric micelles for docetaxel delivery. *J Biomed Mater Res Part A*. 2007;81:847–857. doi:10.1002/jbm.a.31129
133. Men W, Zhu P, Dong S, et al. Layer-by-layer pH-sensitive nanoparticles for drug delivery and controlled release with improved therapeutic efficacy in vivo. *Drug Deliv*. 2020;27:180–190. doi:10.1080/10717544.2019.1709922
134. Mu M, Liang X, Chuan D, et al. Chitosan coated pH-responsive metal-polyphenol delivery platform for melanoma chemotherapy. *Carbohydr Polym*. 2021;264:118000. doi:10.1016/j.carbpol.2021.118000
135. Wen HY, Dong H-Q, Xie W-J, et al. Rapidly disassembling nanomicelles with disulfide-linked PEG shells for glutathione-mediated intracellular drug delivery. *Chem Commun*. 2011;47:3550–3552. doi:10.1039/c0cc04983b
136. Berríos-Caro E, Gifford DR, Galla T. Competition delays multi-drug resistance evolution during combination therapy. *J Theor Biol*. 2021;509:110524. doi:10.1016/j.jtbi.2020.110524
137. Liu W, Ye X, He L, et al. A novel targeted multifunctional nanoplatform for visual chemo-hyperthermia synergy therapy on metastatic lymph nodes via lymphatic delivery. *J Nanobiotechnology*. 2021;19:432. doi:10.1186/s12951-021-01186-8
138. Liu G, Gao N, Zhou Y, et al. Polydopamine-based "four-in-one" versatile nanoplatforms for targeted dual chemo and photothermal synergistic cancer therapy. *Pharmaceutics*. 2019;11:507. doi:10.3390/pharmaceutics11100507
139. Şenel B, Başaran E, Akyıl E, Güven UM, Büyükköroğlu G. Co-delivery of siRNA and docetaxel to cancer cells by NLC for therapy. *ACS Omega*. 2024;9:11671–11685. doi:10.1021/acsomega.3c09098
140. Sharma S, Pukale S, Sahel DK, et al. Folate targeted hybrid lipo-polymeric nanoplexes containing docetaxel and miRNA-34a for breast cancer treatment. *Mater Sci Eng C*. 2021. 128. doi:10.1016/j.msec.2021.112305
141. Swami R, Kumar Y, Chaudhari D, et al. pH sensitive liposomes assisted specific and improved breast cancer therapy using co-delivery of SIRT1 shRNA and docetaxel. *Mater Sci Eng C*. 2021. 120. doi:10.1016/j.msec.2020.111664
142. Dian C, Qian Z, Ran M, Yan X, Dian L. Co-delivery of docetaxel and curcumin functionalized mixed micelles for the treatment of drug-resistant breast cancer by oral administration. *Int J Nanomed*. 2024;19:8603–8620. doi:10.2147/ijn.S472445
143. Ye X, Chen X, He R, et al. Enhanced anti-breast cancer efficacy of co-delivery liposomes of docetaxel and curcumin. *Front Pharmacol*. 2022. 13. doi:10.3389/fphar.2022.969611
144. Zafar S, Akhter S, Garg N, et al. Co-encapsulation of docetaxel and thymoquinone in mPEG-DSPE-vitamin E TPGS-lipid nanocapsules for breast cancer therapy: formulation optimization and implications on cellular and in vivo toxicity. *Eur J Pharm Biopharm*. 2020;148:10–26. doi:10.1016/j.ejpb.2019.12.016
145. Zafar S, Akhter S, Ahmad I, et al. Improved chemotherapeutic efficacy against resistant human breast cancer cells with co-delivery of docetaxel and thymoquinone by chitosan grafted lipid nanocapsules: formulation optimization, in vitro and in vivo studies. *Colloids Surf B*. 2020;186:110603. doi:10.1016/j.colsurfb.2019.110603
146. Alkhatib MH, Bawadud RS, Gashlan HM. Incorporation of docetaxel and thymoquinone in borage nanoemulsion potentiates their antineoplastic activity in breast cancer cells. *Sci Rep*. 2020;10:18124. doi:10.1038/s41598-020-75017-5
147. Tao J, Diao L, Chen F, et al. pH-sensitive nanoparticles codelivering docetaxel and dihydroartemisinin effectively treat breast cancer by enhancing reactive oxidative species-mediated mitochondrial apoptosis. *Mol Pharmaceut*. 2020;18:74–86. doi:10.1021/acs.molpharmaceut.0c00432
148. Ateeq MAM, Aalhate M, Mahajan S, et al. Self-nanoemulsifying drug delivery system (SNEDDS) of docetaxel and carvacrol synergizes the anticancer activity and enables safer toxicity profile: optimization, and in-vitro, ex-vivo and in-vivo pharmacokinetic evaluation. *Drug Delivery Transl Res*. 2023;13:2614–2638. doi:10.1007/s13346-023-01342-7
149. Bhatnagar S, Bankar NG, Kulkarni MV, Venuganti VVK. Dissolvable microneedle patch containing doxorubicin and docetaxel is effective in 4T1 xenografted breast cancer mouse model. *Int J Pharm*. 2019;556:263–275. doi:10.1016/j.ijpharm.2018.12.022
150. Yu Z, Li H, Jia Y, et al. Ratiometric co-delivery of doxorubicin and docetaxel by covalently conjugating with mPEG-poly(β-malic acid) for enhanced synergistic breast tumor therapy. *Polym Chem*. 2020;11:7330–7339. doi:10.1039/d0py01130d
151. Cheng W-J, Lin S-Y, Chuang K-H, et al. Combined docetaxel/pictilisib-loaded mPEGylated nanocarriers with dual HER2 targeting antibodies for synergistic chemotherapy of breast cancer. *Int J Nanomed*. 2022;17:5353–5374. doi:10.2147/ijn.S388066
152. Gao J, Liu J, Xie F, et al. Co-delivery of docetaxel and salinomycin to target both breast cancer cells and stem cells by PLGA/TPGS nanoparticles. *Int J Nanomed*. 2019;14:9199–9216. doi:10.2147/ijn.S230376
153. Qin J, Wang X, Fan G, Lv Y, Ma J. Recent advances in nanodrug delivery system for tumor combination treatment based on photothermal therapy. *Adv Ther*. 2022;6. doi:10.1002/adtp.202200218
154. Duan H, Li L, He S. Advances and prospects in the treatment of pancreatic cancer. *Int J Nanomed*. 2023;18:3973–3988. doi:10.2147/ijn.S413496
155. Zhang L, Yang X, Lv Y, et al. Cytosolic co-delivery of miRNA-34a and docetaxel with core-shell nanocarriers via caveolae-mediated pathway for the treatment of metastatic breast cancer. *Sci Rep*. 2017. 7. doi:10.1038/srep46186
156. Jacob MM, Santhosh A, Rajeev A, et al. Current status of natural products/siRNA co-delivery for cancer therapy. *ChemistrySelect*. 2022. 7. doi:10.1002/slct.202203476
157. Sharma S, Mazumdar S, Italiya KS, et al. Cholesterol and morpholine grafted cationic amphiphilic copolymers for miRNA-34a delivery. *Mol Pharm*. 2018;15:2391–2402. doi:10.1021/acs.molpharmaceut.8b00228
158. Kim EJ, Um SJ. SIRT1: roles in aging and cancer. *BMB Rep*. 2008;41:751–756. doi:10.5483/bmbrep.2008.41.11.751
159. Chen L, Qian M, Zhang L, et al. Co-delivery of doxorubicin and shRNA of Beclin1 by folate receptor targeted pullulan-based multifunctional nanomicelles for combinational cancer therapy. *RSC Adv*. 2018;8:17710–17722. doi:10.1039/c8ra01679h
160. Wang Z, Chen W. Emerging roles of SIRT1 in cancer drug resistance. *Genes Cancer*. 2013;4:82–90. doi:10.1177/1947601912473826

161. Jin X, Wei Y, Xu F, et al. SIRT1 promotes formation of breast cancer through modulating Akt activity. *J Cancer*. 2018;9:2012–2023. doi:10.7150/jca.24275
162. Ma Z, Fan Y, Wu Y, et al. Traditional Chinese medicine-combination therapies utilizing nanotechnology-based targeted delivery systems: a new strategy for antitumor treatment. *Int J Nanomed*. 2019;14:2029–2053. doi:10.2147/ijn.S197889
163. Barcelos KA, Mendonça CR, Noll M, et al. Antitumor properties of curcumin in breast cancer based on preclinical studies: a systematic review. *Cancers*. 2022;14:2165. doi:10.3390/cancers14092165
164. Barkat MA, Harshita, Ahmad J, et al. Insights into the targeting potential of thymoquinone for therapeutic intervention against triple-negative breast cancer. *Curr Drug Targets*. 2018;19:70–80. doi:10.2174/1389450118666170612095959
165. Rajput S, Kumar BNP, Sarkar S, et al. Targeted apoptotic effects of thymoquinone and tamoxifen on XIAP mediated Akt regulation in breast cancer. *PLoS One*. 2013;8:e61342. doi:10.1371/journal.pone.0061342
166. Li Y, Wang W, Li A, et al. Dihydroartemisinin induces pyroptosis by promoting the AIM2/caspase-3/DFNA5 axis in breast cancer cells. *Chem Biol Interact*. 2021;340:109434. doi:10.1016/j.cbi.2021.109434
167. Chen K, Shou L-M, Lin F, et al. Artesunate induces G2/M cell cycle arrest through autophagy induction in breast cancer cells. *Anti-Cancer Drugs*. 2014;25:652–662. doi:10.1097/cad.0000000000000089
168. Mari A, Mani G, Nagabhishek SN, et al. Carvacrol promotes cell cycle arrest and apoptosis through PI3K/AKT signaling pathway in MCF-7 breast cancer cells. *Chin J Integr Med*. 2021;27:680–687. doi:10.1007/s11655-020-3193-5
169. Verret B, Cortes J, Bachelot T, Andre F, Arnedos M. Efficacy of PI3K inhibitors in advanced breast cancer. *Ann Oncol*. 2019;30:x12–x20. doi:10.1093/annonc/mdz381
170. Wallin JJ, Guan J, Prior WW, et al. GDC-0941, a novel class I selective PI3K inhibitor, enhances the efficacy of docetaxel in human breast cancer models by increasing cell death in vitro and in vivo. *Clin Cancer Res*. 2012;18:3901–3911. doi:10.1158/1078-0432.Ccr-11-2088
171. Vuylsteke P, Huizing M, Petrakova K, et al. Pictilisib PI3Kinase inhibitor (a phosphatidylinositol 3-kinase [PI3K] inhibitor) plus paclitaxel for the treatment of hormone receptor-positive, HER2-negative, locally recurrent, or metastatic breast cancer: interim analysis of the multicentre, placebo-controlled, phase II randomised PEGGY study. *Ann Oncol*. 2016;27:2059–2066. doi:10.1093/annonc/mdw320
172. Yao E, Zhou W, Lee-Hoeflich ST, et al. Suppression of HER2/HER3-mediated growth of breast cancer cells with combinations of GDC-0941 PI3K inhibitor, trastuzumab, and pertuzumab. *Clin Cancer Res*. 2009;15:4147–4156. doi:10.1158/1078-0432.Ccr-08-2814
173. Zhong P, Chen X, Guo R, et al. Folic acid-modified nanoerythrocyte for codelivery of paclitaxel and tariquidar to overcome breast cancer multidrug resistance. *Mol Pharm*. 2020;17:1114–1126. doi:10.1021/acs.molpharmaceut.9b01148
174. Saneja A, Dubey RD, Alam N, Khare V, Gupta PN. Co-formulation of P-glycoprotein substrate and inhibitor in nanocarriers: an emerging strategy for cancer chemotherapy. *Curr Cancer Drug Targets*. 2014;14:419–433. doi:10.2174/1568009614666140407112034
175. Kim CH, Lee S, Choi JY, et al. Functionalized lipid nanocarriers for simultaneous delivery of docetaxel and tariquidar to chemoresistant cancer cells. *Pharmaceuticals*. 2023. 16. doi:10.3390/ph16030349
176. Dewangan J, Srivastava S, Rath SK. Salinomycin: a new paradigm in cancer therapy. *Tumour Biol*. 2017;39:1010428317695035. doi:10.1177/1010428317695035
177. Wang H, Zhang H, Zhu Y, et al. Anticancer mechanisms of salinomycin in breast cancer and its clinical applications. *Front Oncol*. 2021;11:654428. doi:10.3389/fonc.2021.654428
178. Kim JH, Yoo HI, Kang HS, Ro J, Yoon S. Salinomycin sensitizes antimitotic drugs-treated cancer cells by increasing apoptosis via the prevention of G2 arrest. *Biochem Biophys Res Commun*. 2012;418:98–103. doi:10.1016/j.bbrc.2011.12.141
179. Ashrafizadeh M, Zarrabi A, Bigham A, et al. (Nano)platforms in breast cancer therapy: drug/gene delivery, advanced nanocarriers and immunotherapy. *Med Res Rev*. 2023;43:2115–2176. doi:10.1002/med.21971
180. Luo W, Ali YF, Liu C, et al. Particle therapy for breast cancer: benefits and challenges. *Front Oncol*. 2021;11:662826. doi:10.3389/fonc.2021.662826
181. Jo MJ, Lee YJ, Park C-W, et al. Evaluation of the physicochemical properties, pharmacokinetics, and in vitro anticancer effects of docetaxel and osthol encapsulated in methoxy poly(ethylene glycol)-b-poly(caprolactone) polymeric micelles. *Int J Mol Sci*. 2020;22:231. doi:10.3390/ijms22010231
182. Zhang L, Zhang N. How nanotechnology can enhance docetaxel therapy. *Int J Nanomed*. 2013;8:2927–2941. doi:10.2147/ijn.S46921
183. Ahmad A, Sheikh S, Taran R, et al. Therapeutic efficacy of a novel nanosomal docetaxel lipid suspension compared with taxotere in locally advanced or metastatic breast cancer patients. *Clin Breast Cancer*. 2014;14:177–181. doi:10.1016/j.clbc.2013.09.011
184. Subramanian S, Prasanna R, Biswas G, et al. Nanosomal docetaxel lipid suspension-based chemotherapy in breast cancer: results from a multicenter retrospective study. *Breast Cancer*. 2020;12:77–85. doi:10.2147/bctt.S236108
185. Swain SM, Miles D, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, Phase 3 study. *Lancet Oncol*. 2020;21:519–530. doi:10.1016/s1470-2045(19)30863-0
186. Souri M, Soltani M, Moradi Kashkooli F, et al. Towards principled design of cancer nanomedicine to accelerate clinical translation. *Mater Today Bio*. 2022;13:100208. doi:10.1016/j.mtbio.2022.100208
187. Zhang D, Zhai B, Sun J, et al. Advances on delivery system of active ingredients of dried toad skin and toad venom. *Int J Nanomed*. 2024;19:7273–7305. doi:10.2147/ijn.S469742
188. Zhang P, Xiao Y, Sun X, et al. Cancer nanomedicine toward clinical translation: obstacles, opportunities, and future prospects. *Med*. 2023;4:147–167. doi:10.1016/j.medj.2022.12.001
189. Hajimolaali M, Dorkoosh FA, Antimisiaris SG. Review of recent preclinical and clinical research on ligand-targeted liposomes as delivery systems in triple negative breast cancer therapy. *J Liposome Res*. 2024;34:671–696. doi:10.1080/08982104.2024.2325963
190. Gessner I. Optimizing nanoparticle design and surface modification toward clinical translation. *MRS Bulletin*. 2021;46:643–649. doi:10.1557/s43577-021-00132-1
191. Zhang L, Zhou Y, Chai X, et al. Excipient-free prodrug-based three-in-one nanoparticles co-deliver diversified agents to amplify tumor therapy. *Chem Eng J*. 2022;435:134880. doi:10.1016/j.cej.2022.134880
192. Mu M, Liang X, Zhao N, et al. Boosting ferroptosis and microtubule inhibition for antitumor therapy via a carrier-free supermolecule nanoreactor. *J Pharm Anal*. 2023;13:99–109. doi:10.1016/j.jpha.2022.09.003

193. Nezhadi S, Dorkoosh FA. Co-delivery systems: hope for clinical application? *Drug Deliv Translat Res*. 2021;12:1339–1354. doi:10.1007/s13346-021-01041-1
194. Ma Y, Wang X, Liao Y-P, et al. Nanomaterials in the diagnosis and treatment of ophthalmic diseases. *Nano Today*. 2024. 54. doi:10.1016/j.nantod.2023.102117
195. Gonzalez-Valdivieso J, Girotti A, Schneider J, Arias FJ. Advanced nanomedicine and cancer: challenges and opportunities in clinical translation. *Int J Pharm*. 2021;599:120438. doi:10.1016/j.ijpharm.2021.120438