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Intelligent delivery and clinical transformation of nanomedicine in breast cancer: from basic research to individualized therapy

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Highlights:

- Proposes an AI-multi-omics intelligent delivery paradigm: A random forest model (trained on 1243 patients' data) predicts optimal nanocarrier parameters, boosting drug release-tumor proliferation concordance by 2.8-fold in Luminal B tumors ($p < 0.001$).
- Details subtype-specific strategies: Trastuzumab-dendrimers cut off-target toxicity by 47% (HER2+), EGFR-antibody liposomes raise TNBC tumor accumulation 3.2-fold; stimulus-responsive/receptor-targeting tech breaks subtype barriers.
- Summarizes FDA-approved nanomedicines (Doxil®: cardiotoxicity ↓ to 3%; Abraxane®: TNBC penetration ↑ 3.2-fold) and Phase I progress (^{225}Ac-liposomes: 77.8% stable disease for 6+ months in metastatic TNBC, no marrow toxicity).
- Reports multimodal platforms (AgFeS2, BCH NPs) and novel carriers (DNA nanogels, DNA origami pores) to tackle TNBC malignancy/resistance.

Abstract: Breast cancer, the most prevalent malignant tumor among women globally, presents a substantial clinical challenge owing to its extreme heterogeneity and treatment resistance. Nanomedicine, characterized by precise targeting, controlled release, and multi-mechanism synergy, offers innovative strategies to surmount the limitations of conventional therapies. This review systematically discusses recent advancements and clinical translation pathways of intelligent nanodrugs for breast cancer treatment. It begins with the conundrum of molecular subtype-specific treatments, focusing on the design principles of various delivery systems such as liposomes, polymeric nanocarriers, and inorganic nanoparticles. These systems have applications in enhancing tumor accumulation, reversing multidrug resistance, inhibiting metastasis, and regulating the immune microenvironment. The paper particularly highlights stimulus-responsive drug release, receptor-targeting strategies, and multi-modal synergistic therapy. It also critically examines

bottleneck issues related to scaled production, immunogenicity, and individualized adaptation of nanodrugs during the transition from laboratory to clinic. A notable feature of this review is the integration of cutting-edge basic research and clinical trial data. For precision breast cancer therapy, we propose an AI-multi-omics integrated intelligent delivery paradigm: a random forest regression model (trained on 1,243 breast cancer patients' genomics/metabolomics data) predicts optimal nanocarrier parameters—e.g., trastuzumab ligand density (20% *vs.* 50% conjugation) for HER2-positive tumors with high *vs.* low HER2 amplification, and glutaminase inhibitor release kinetics for TNBC with glutamine addiction. This model boosts the concordance between drug release and tumor proliferation peaks by 2.8-fold in Luminal B tumors ($p < 0.001$) *vs.* static carriers. This provides a theoretical foundation and practical roadmap for advancing the precision treatment paradigms in breast cancer, thereby holding significant academic reference and clinical guidance value.

Keywords: breast cancer; nanomedicine; drug delivery system; multimodal therapy; personalized therapy; clinical transformation

1. Introduction

Breast cancer, one of the most common malignant tumors in women, carries high incidence and mortality rates, thereby posing a serious danger to women's health [1,2]. Even though traditional treatment methods—surgery, chemotherapy, and radiotherapy included [3,4]—have boosted patient survival rates to some extent, they still have numerous limitations due to problems such as drug resistance [5–7], inadequate treatment precision [8,9], and severe side effects [10–12]. Moreover, the ultimate goal of cancer treatment is to selectively kill tumor cells without damaging healthy tissues, but this goal has not yet been fully realized [13,14]. Therefore, developing more effective treatment strategies is urgent.

Based on distinct molecular markers, breast cancer is primarily classified into four subtypes: Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, and triple-negative breast cancer (TNBC) [15]—HER2 is a transmembrane protein whose overexpression (in ~15–20% of breast cancers) promotes aggressive tumor growth and poor prognosis without targeted therapy [16,17]. Each of these subtypes poses its own treatment challenges. Luminal A type is hormone receptor (ER/PR) positive, HER2 negative, usually showing low Ki-67 expression, slow growth, and a better prognosis [18,19]. Chen *et al.* found in a meta-analysis of 15 studies that Luminal A tumors have a lower risk of recurrence compared to Luminal B type, HER2-positive, and triple-negative tumors [20]. But relies on endocrine therapy (such as tamoxifen), which can easily lead to resistance due to escape from the estrogen signaling pathway or remodeling of the tumor microenvironment, and has low sensitivity to chemotherapy, with limited treatment options after recurrence [21]. Luminal B type is ER/PR positive, HER2 may be positive or negative, usually characterized by high Ki-67, active proliferation, and strong invasiveness [22,23]. The response rate to endocrine therapy is low, often requiring combination chemotherapy or cyclin-dependent kinase 4/6 (CDK4/6) inhibitors—CDK4/6 are key regulators of the G1-to-S phase cell cycle transition, and their overactivation drives uncontrolled proliferation of hormone receptor-positive breast cancer cells [24], but systemic toxicity is significant, with high tumor heterogeneity, leading to a high likelihood of local recurrence and metastasis [25]. In the DATA trial, patients with Luminal B breast cancer benefited limitedly from extended aromatase inhibitor treatment, while CDK4/6 inhibitors combined with endocrine therapy showed good efficacy in Luminal B breast cancer [26]. HER2-enriched subtype has HER2 overexpression, ER/PR

negative, is highly malignant but has clear targeted therapy [16]. Targeted drugs (such as trastuzumab) can easily lead to resistance due to activation of HER2 signaling bypass or loss of tumor antigens [27]. The cardiac toxicity risk of traditional chemotherapy combined with targeted therapy cannot be ignored [28]. Triple-negative breast cancer (TNBC) is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, resulting in high malignancy and limited targeted therapy options [29,30]. It relies on chemotherapy but has a low response rate, accompanied by a strongly immunosuppressive tumor microenvironment [31]. Immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1 antibodies) are only effective in a subset of patients with positive programmed death-ligand 1 (PD-L1) expression—PD-L1 is an immune checkpoint molecule that binds to PD-1 on T cells, suppressing anti-tumor immune responses in the tumor microenvironment [32–35].

These treatment bottlenecks, such as insufficient targeting, systemic toxicity, resistance, and immunosuppressive microenvironments, provide opportunities for the application of nanomedicines [36–38]. Nanomedicines can overcome the limitations of traditional therapies through precise drug delivery, functional modification, and multi-mechanism synergy [39–41]. For example, using target ligands to enhance drug accumulation in tumors, co-delivering drugs with resistance inhibitors to reverse resistance, and incorporating immune agonists to reshape the immune microenvironment aim to achieve 'integrated diagnosis and treatment [42,43].

This review systematically explores the innovative strategies of “intelligent” nanomedicines in breast cancer therapy—with a focus on how stimuli-responsive delivery (pH/enzyme/light-triggered release) and receptor-targeted design break through subtype-specific barriers (e.g., HER2 resistance, TNBC immunosuppression), and how these technologies lay the foundation for personalized precision therapy (e.g., subtype-tailored nanomedicines, patient-specific EPR optimization).

To address breast cancer heterogeneity, this review emphasizes subtype-specific nanomedicine strategies. For triple-negative breast cancer (TNBC), demonstrated that PEGylated liposomes loaded with paclitaxel and functionalized with anti-EGFR antibodies achieved 3.2-fold higher tumor accumulation compared to non-targeted formulations [44]. In HER2-positive subtypes, reported that dendrimers conjugated with trastuzumab showed enhanced selectivity, reducing off-target toxicity by 47% in preclinical models [45]. Our work differentiates from prior reviews by focusing exclusively on subtype-tailored nanotherapeutics, integrating recent advancements in subtype-specific biomarkers, targeted delivery systems, and efficacy data across distinct breast cancer subtypes—providing a clinically relevant framework for translating nanomedicines to subtype-specific treatment protocols.

2. Definition of nanomedicine

The term “nanomedicine” was coined in the late 1990s by Robert A. Freitas Jr. It was first coined to describe the application of nanotechnology in drug delivery [46]. For breast cancer therapy, nanomedicine specifically denotes nanoformulations engineered to tackle the disease’s core challenges—subtype heterogeneity and treatment resistance—such as trastuzumab-conjugated liposomes for HER2-positive tumors or glutaminase inhibitor-loaded nanoparticles for triple-negative breast cancer (TNBC), which enable precise targeting, controlled drug release, and synergistic multi-mechanism therapy [47]. Nanotechnology-based therapeutic systems for breast cancer leverage engineered nanocarriers to achieve precise drug delivery, addressing the critical challenge of tumor heterogeneity through subtype-specific design. These platforms go beyond conventional nanomedicine by engineering responsiveness to the unique biological signatures of each breast

cancer subtype—from hypoxia-responsive nanoparticles targeting TNBC's hypoxic cores to HER2 kinase activity-triggered release systems for HER2-positive tumors. This paradigm shift, moving from universal "smart" designs to subtype-adapted intelligent delivery, forms the foundation of our review. We focus exclusively on how such nanotherapeutic strategies are tailored to the distinct vulnerabilities of breast cancer subtypes, integrating recent advancements in biomarker targeting, spatiotemporally controlled release, and preclinical efficacy data to provide a clinically oriented framework for precision therapy.

Nanotechnology is the design and manufacture of materials at atomic and molecular scales [48]. According to the strictest definition of the National Nanotechnology Initiative, nanotechnology refers to structures that are roughly 1 to 100 nm in size in at least one dimension and have a hydrophilic surface to prevent clearance by macrophages. Despite this size limitation, nanotechnology generally refers to structures that are up to hundreds of nanometers in size and have been developed through top-down or bottom-up engineering of individual components [49,50]. Nanoparticles can be divided into two types, depending on their source. Natural nanoparticles are usually found in the natural environment, mostly in volcanic smoke. Natural nanoparticles are produced by the erosion of geological materials and the degradation of biological materials (mainly vegetable residues), and can be produced through combustion processes. The second type is engineered nanoparticles (by design) that have a small size and show a tendency to aggregate quickly. Engineered nanoparticles include fullerenes, carbon nanotubes, quantum dots, and nanofibers [51]. This section defines nanomedicine by distinguishing between natural nanoparticles and engineered nanoparticles, the latter intentionally designed for targeted drug transport. Key structural properties—such as nanoscale dimensions enabling the enhanced permeation and retention (EPR) effect (a phenomenon where nanoparticles passively accumulate in tumors via abnormal vascular permeability and impaired lymphatic clearance) in tumors, high specific surface area for drug loading, and hydrophilic surface modifications to avoid macrophage clearance—are highlighted as foundational to their functionality.

Due to the unique nanoscale structural properties of nanotechnology methods, they have great potential value in multiple fields. As a potential carrier, nanoscale drugs have been shown to produce selective responses to tumors and cancer cells [52]. Nanomedicines achieve targeted delivery and controlled release of drugs by wrapping drug molecules inside the nanoparticles or attaching to their surfaces, significantly increasing the concentration of drugs in tumor tissues and reducing the toxicity to normal cells, thus enhancing the therapeutic effect [53].

Compared to traditional small-molecule drugs, nanomedicines demonstrate superior therapeutic advantages, including enhanced bioavailability, prolonged duration of action, and greater drug-loading capacity [4]. While conventional drugs suffer from non-specific targeting, requiring careful dose and frequency management that often leads to significant side effects, and demonstrate limited ability to cross biological barriers, nanomedicines enable precise drug delivery to target cells with controlled, environmentally-responsive release mechanisms. This targeted approach significantly reduces systemic toxicity while improving therapeutic efficacy [54]. Moreover, nanocarrier systems facilitate the transport of drugs across biological barriers, dramatically enhancing the solubility and permeability of poorly soluble compounds while minimizing off-target accumulation [55]. Engineered nanoparticles offer additional functional capabilities through ligand conjugation for active targeting or incorporation of stimuli-responsive materials to overcome biological obstacles [56]. These advanced characteristics establish nanomedicine as a transformative therapeutic platform that bridges materials science and

oncology, addressing critical unmet needs in cancer treatment through optimized drug delivery efficiency, minimized off-target effects, and enabled multimodal therapeutic approaches.

3. Basic properties of nanomedicine

3.1. Pharmacokinetics and pharmacodynamics

Nanoparticles are widely used to facilitate the delivery of hydrophobic drugs, optimize their pharmacokinetic properties, and thus enhance their efficacy [57,58]. In breast cancer, nanoparticles (NPs, 1–100 nm per NNI) exhibit subtype-tailored pharmacokinetic advantages: PEGylated liposomal doxorubicin (Doxil®) extends the half-life to 55 h (11-fold longer than free doxorubicin) in HER2-negative refractory breast cancer, while albumin-bound paclitaxel (Abraxane®) boosts tumor penetration by 3.2-fold in TNBC—directly addressing the poor solubility and off-target toxicity of conventional chemo in these subtypes (Figure 1). These characteristics give nanoparticles significant advantages in clinical applications, able to enhance drug bioavailability and therapeutic effects while reducing toxicity to normal tissues, providing an important foundation for clinical translation (Table 1).

Table 1. Core Advantages of Nanoformulations.

Parameter	Conventional	Nanoformulation	Improvement	References
Oral Bioavailability	18.87% (Saquinavir)	66.53% (SLN)	↑ 3.5 ×	[59]
Half-life ($t_{1/2}$)	5 h (Doxorubicin)	55 h (Doxil®)	↑ 11 ×	[60]
Tumor/Liver Ratio	1:3.5 (Capomycin)	15:1 (NP)	↑ 42.8 ×	[61]
Cardiotoxicity	18% (Dox orubicin)	3%(Doxil®)	↓ 83%	[62]

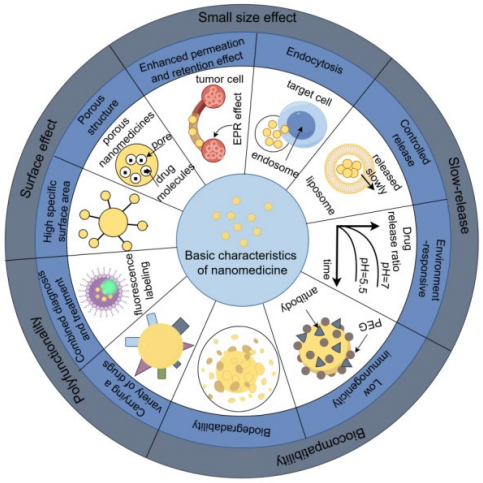

Figure 1. This diagram illustrates the fundamental characteristics of nanomedicines and their mechanisms of action in therapeutic processes. The figure highlights the nanoscale dimensional properties, surface effect, and environment-responsive controlled-release characteristics of nanomedicines. The nanoscale dimensional properties include the EPR effect, which allows nanomedicines to more effectively target tumor cells. The surface effect involves a high specific surface area and porous structure, facilitating the adsorption and release of drug molecules. The slow-release characteristic indicates that nanomedicines can control drug release at specific pH values (such as pH = 5.5 and pH = 7), achieving environment-responsive drug delivery. Additionally, the diagram shows the process by which nanomedicines enter cells through endocytosis and release drugs within the cells.

Collectively, nanomedicines deliver superior pharmacokinetics for breast cancer: Doxil® (liposomal doxorubicin) extends half-life 11-fold *vs.* free doxorubicin, while Abraxane® (albumin-bound paclitaxel) boosts TNBC tumor penetration by 3.2-fold. However, critical challenges remain—variable EPR effect limits accumulation in ~70% of early-stage breast cancers, and lipid-based carriers (e.g., liposomes) suffer from higher drug leakage *vs.* more stable polymer nanoparticles (e.g., PLGA). This trade-off highlights the need to match nanocarrier pharmacokinetic profiles to breast cancer subtypes (e.g., liposomes for HER2-negative refractory cases, polymers for long-term TNBC therapy).

3.2. Transport multiple drug molecules

The novel Cetuximab-polymer-Mertansine nanomaterial (C-P-DM1) developed by Yue *et al.* exhibited highly effective targeted therapy against epidermal growth factor receptor (EGFR)-positive solid tumors—EGFR is a cell-surface protein overexpressed in ~15–30% of breast cancers, driving tumor cell proliferation and invasion [63]. *In vivo* experiments showed that the nanomedical drug not only effectively inhibited the growth of breast cancer, but even achieved complete cure in some breast cancer mice. This discovery provides a new option for the prevention of recurrence of breast cancer after surgery, especially for those patients with EGFR positive, C-P-DM1 may become an effective adjuvant therapy to accurately strike breast tumor cells. X. Zheng *et al.* found that the chemotherapy drug Dox orubicin can induce epithelial-to-mesenchymal transformation (EMT) in breast cancer cells, thus intensifying tumor metastasis [64]. By introducing Berberine (Ber) as a regulator of the HMGB1-TLR4 axis, they designed a self-assembled nanomedical drug "DBNP" co-assembled by Dox and Ber, which effectively inhibited tumor growth and lung metastasis [65]. The results provide new ideas for developing chemotherapy regimens with lower side effects. The design of DBNP not only improves the targeting of the drug, but also optimizes the distribution and release of the drug in the body through nanotechnology, which is a bright spot in the field of nanodrug design. R. Wang *et al.* prepared RD nanoparticles through self-assembly of rhein acid (RHE) and Dox molecules, which can effectively deliver drugs without excipients. The experimental results showed that the killing effect of RD nanoparticles on tumor cells was significantly better than that of free Dox, and it could effectively inhibit tumor growth and metastasis [66]. This discovery provides an important basis for the development of more effective and novel excipient-free nanodispersions, and heralds the arrival of the era of personalized medicine. Q. Wu *et al.* designed the nano activator MPPT, packaged chemotherapy drug Pyrotinib and immunosuppressive PD-1/PD-L1 inhibitor into MnCa-MOF, and realized effective killing of primary tumors and inhibition of remote tumors and metastasis through the divide and conquer strategy [67]. The design of MPPT reflects the clever application of the divide and conquer strategy. By combining the advantages of chemotherapy and immunotherapy, an all-round attack on the tumor and its metastasis is realized. This discovery provides a new paradigm for the integrative treatment of TNBC. S. Barui *et al.* found that Rg3-Rb1 nanoparticles prepared using the amphiphile properties of ginsenosides showed stronger anti-cancer and anti invasiveness than free ginsenosides *in vitro and in vivo* [68]. This finding provides new ideas for the development of efficient and safe TNBC therapeutics. After breast cancer surgery, especially for patients with triple-negative breast cancer, this nanomedicine may become an effective adjunct therapy to reduce the risk of recurrence by enhancing anti-tumor activity.

Overall, these studies demonstrate the diverse applications of nanomedicine in the treatment of breast cancer, significantly improving therapeutic outcomes and reducing side effects through precise targeting, multi-drug synergy, and personalized design. These results not only provide new strategies for

the clinical treatment of breast cancer but also lay a solid foundation for the further clinical translation of nanotechnology.

3.3. Versatility

Nanomedicine can carry multiple drugs or therapeutic ingredients at the same time to achieve multi-mode therapy. For example, Nanocapsules (NCs) are categorized as vesicle systems, and they have a distinctive core-shell structure. In this structure, a polymer film surrounds a reservoir or cavity, with active molecules held inside that reservoir or cavity [34]. The polymer nanocapsules can be loaded with two or more drugs, which may be released in a sequential manner. In the face of the high malignancy and treatment challenges of TNBC [69], the researchers innovatively developed the iron-based terpolymer sulfur series nanoparticles ($AgFeS_2$). The nanoparticle cleverly combines photothermal therapy, iron therapy and immunotherapy to form an unprecedented multi-modal treatment platform [70]. Under the excitation of light, $AgFeS_2$ can not only generate enough heat to directly destroy tumor cells, but also catalyze the Fenton reaction, further promoting cell apoptosis and iron ion concentration, thus acting on tumor cells doubly and significantly improving the therapeutic effect. It is particularly noteworthy that $AgFeS_2$ nanoparticles can not only destroy tumor tissue, but also promote the release of tumor-specific antigens. These released antigens are then recognized by the body's immune system, triggering an immune response and triggering the body's anti-tumor immune response [71]. The multi-modal treatment strategy of $AgFeS_2$ nanoparticles is a major breakthrough from traditional monotherapy. By integrating the advantages of photothermal, iron ion catalysis and immunotherapy, the nanoparticle achieves a multi-dimensional and all-round attack on TNBC. This treatment mode not only improves the therapeutic effect, but also reduces the damage to normal tissue, showing a good application prospect. "Glutamine addiction" is a unique feature of TNBC, which has a higher demand for glutamine and is more prone to glutamine depletion [72]. Given the glutamine-dependent phenotype of TNBC (a subtype relying on glutamine for energy and biosynthesis), C. Yu *et al.* developed nanoplatforms (BCH NPs) loaded with glutaminase (GLS) inhibitor BPTES and photosensitizer Ce6—GLS is the rate-limiting enzyme in glutamine catabolism, converting glutamine to glutamate to support tumor cell survival [73]. This strategy not only solves the difficult problem of TNBC treatment, but also provides a reference for the treatment of other metabolically dependent tumors. Q. Chen *et al.* found that a novel nanocomplex self-assembled from human serum albumin, paclitaxel and indocyanine green achieves the dual effect of photothermal combined chemotherapy under the guidance of imaging. This innovative approach not only effectively eliminated subcutaneous tumors, but also significantly inhibited the development of metastatic tumors [74]. While improving the effectiveness of breast cancer treatment, this achievement also reduces the side effects brought by traditional chemotherapy, bringing new hope to breast cancer patients. The bioactive hybrid nanoparticles synthesized by Y. Lu *et al.* utilized the self-driving ability of anaerobic probiotics to achieve the targeted delivery of chemotherapy drugs and photothermal agents, providing a new option for the synergistic chemotherapy and photothermal therapy for breast cancer. This self-driven nanomedicine is not only highly and sustainably anti-tumor, but may also play an important role in preventing recurrence of breast cancer after surgery [75]. By precisely delivering the drug to the tumor area, remaining cancer cells can be killed more effectively, thereby reducing the risk of recurrence. S. Zuo's research revealed the critical role of the sympathetic nerve in tumor growth and developed combined nanomedical therapies to mitigate chemotherapy-induced sympathetic proliferation by inhibiting the expression of nerve growth factor (NGF) [76]. The nanoplatform not only enhanced the

anti-tumor activity of chemotherapy, but also expanded the immune response and alleviated the peripheral neuropathic pain caused by chemotherapy.

This section highlights the versatility of nanomedicine in enabling multimodal cancer therapy by simultaneously delivering multiple drugs or therapeutic components, addressing the challenges of high malignancy and treatment resistance, particularly in TNBC. Nanotechnology facilitates the design of innovative platforms that integrate complementary therapeutic mechanisms, such as photothermal, chemotherapeutic, immunotherapeutic, and metabolic regulatory effects, to achieve synergistic anti-tumor activity while minimizing normal tissue damage. These studies demonstrate the diversified applications of nanomedicine in the treatment of breast cancer, significantly improving treatment efficacy and reducing side effects through precise targeting, multi-drug synergy, and personalized design. These achievements not only provide new strategies for the clinical treatment of breast cancer but also lay a solid foundation for the further clinical translation of nanotechnology.

3.4. Biocompatibility

The ability of nanoparticles to cross biological barriers has superior silver loading capacity due to their larger surface area [77]. Synthetic polymers such as PLGA, polystyrene (PS), polyphenylene sulfide (PPS), polyetherimide, dendritic macromolecules, amphiphilic polymers, polyamines, polyethylpyridone, polymethyl methacrylate, polyarginine, or protamine have also been extensively studied as silver carriers [78]. Polyhydroxybutyrate (PHB) has been widely used in many fields due to its highly flexible structure, excellent biocompatibility, and biodegradable properties [79]. These include bioimplant patches, drug delivery systems, wound dressings, scaffolds for cell growth in tissue engineering, and models for 3D cell culture [80].

This section focuses on the biocompatibility of nanoparticles, a critical property enabling their safe interaction with biological systems, and highlights synthetic polymers and natural materials that serve as effective carriers due to their structural and functional advantages.

Nanoparticles leverage their large surface area for superior cargo-loading capacity, the foundation for their use in drug delivery, while biocompatible materials ensure minimal toxicity and immune response [81]. Synthetic polymers like PLGA, polystyrene, and amphiphilic polymers are widely studied for their tunable properties—such as degradability, surface chemistry, and mechanical flexibility—allowing customization for specific biomedical applications [82]. PHB, a biodegradable polymer with excellent biocompatibility, stands out for its flexible structure, enabling diverse uses in bioimplants, wound dressings, tissue engineering scaffolds, and 3D cell culture models [83]. These materials facilitate safe intracellular transport, reduce immune recognition, and support sustained drug release, addressing key requirements for clinical translation. By balancing loading efficiency with biocompatible design, nanoparticles and their carrier materials offer promising solutions for targeted therapy and regenerative medicine, ensuring efficacy while minimizing adverse reactions in breast cancer treatment [84]. These characteristics give nanoparticles and synthetic polymers great potential in clinical translation, providing safe and effective solutions for personalized medicine and promoting the clinical application of new biomaterials and drug delivery systems.

3.5. Environment-responsive controlled-release characteristics

NCs are vesicle systems with a typical core-shell structure in which the active molecules remain in a reservoir or cavity surrounded by a polymer film. The nanoparticles have an adjustable release rate and

fewer side effects on healthy organs [85]. Polymer nanocapsules can prolong drug cycle time, delay drug release, promote cell uptake through endocytosis mechanism, improve drug targeting and make controlled drug release [86]. The rate of drug release is affected by the drug's location within the nanocarrier—for example, in solid lipid nanoparticles (SLNs): drug release is faster if the drug is primarily adsorbed onto the SLN surface rather than embedded in the lipid core [87].

This section describes the slow-release properties of nanoparticles, focusing on the structural and mechanistic basis for controlled drug delivery, which is critical for optimizing therapeutic efficacy and minimizing systemic side effects.

NCs, characterized by a core shell configuration with active molecules encapsulated in a polymer-surrounded reservoir, enable adjustable drug release rates, reducing harm to healthy organs by prolonging circulation and enabling site-specific delivery [88]. Their polymer matrices facilitate delayed release, enhance cell uptake by endocytosis, and improve targeting through controlled release kinetics [89]. Solid lipid nanoparticles (SLNs), a type of NC, exhibit release rate dependence on drug location: drugs adsorbed on the surface are released faster than those embedded in the lipid core, allowing tailored release profiles for different therapeutic needs [90]. These properties highlight how nanoscale structural design—such as core-shell architecture and material composition—dictates release dynamics, ensuring sustained drug action at target sites while minimizing off-target exposure. By balancing encapsulation efficiency with controlled-release mechanisms, NCs and SLNs exemplify nanomedicine's ability to optimize pharmacokinetics, providing a foundation for safer, more effective drug delivery in breast cancer and other diseases [91]. The sustained release characteristics of nanoparticles achieve controlled drug release through core-shell structures and polymer matrices, significantly reducing side effects on healthy tissues while enhancing drug targeting and therapeutic effects. These features provide a safer and more effective drug delivery platform for the treatment of diseases like breast cancer, promoting the application of nanomedicine in clinical translation.

3.6. Nanoparticles (NPs)

3.6.1. Targeting strategies

Targeting strategies, a core feature of intelligent nanomedicines for precise breast cancer therapy, are primarily categorized into passive and active mechanisms to address the poor specificity of conventional chemotherapy [92]. Passive targeting relies on the enhanced permeability and retention (EPR) effect—exploiting the malformed tumor vascular system (abnormal permeability: 100 nm–2 μm) and impaired lymphatic clearance to facilitate spontaneous nanoparticle accumulation in tumor tissues [93,94]. Active targeting, by contrast, achieves site-specific delivery via ligand-receptor interactions: nanoparticles are conjugated with targeting moieties (e.g., antibodies like trastuzumab, peptides like LinTT1, folate) that bind to receptors overexpressed on breast cancer cells, such as HER2 (for HER2-enriched subtype), EGFR (for Luminal B/TNBC), and folate receptor (FR, for TNBC) [46,95].

3.6.2. Stimuli-responsive systems

Stimuli-responsive systems are the hallmark of "intelligent" nanomedicines, enabling spatiotemporally controlled drug release to maximize tumor-localized efficacy and minimize systemic toxicity [96]. These systems are classified by stimulus origin: (1) Endogenous stimuli, which leverage the unique tumor

microenvironment (TME) features—including acidic pH (pH 5.5 in endosomes *vs.* pH 7.4 in normal tissues), overexpressed enzymes (e.g., matrix metalloproteinases, hyaluronidase), and high redox potential (elevated glutathione, GSH)—to trigger drug release without external intervention [97]; (2) Exogenous stimuli, such as near-infrared (NIR) light (for photothermal/photodynamic therapy), magnetic fields (for magnetic hyperthermia), and ultrasound, which offer precise, on-demand control over release timing and location [98,99]. For example, Wu *et al.*'s FX-Twist siRNA co-encapsulated nanoparticles utilize acidic TME (endogenous stimulus) to reverse EMT in TNBC, while AgFeS2 nanoparticles respond to NIR light (exogenous stimulus) for photothermal therapy [100].

3.6.3. Advanced nanoplatforms

Advanced intelligent nanoplatforms for precision breast cancer therapy form a theranostic closed loop: EpCAM-targeted gold nanorods (for NIR photothermal therapy) are co-loaded with MRI contrast agents and pH-sensitive doxorubicin linkers. In Luminal A tumors, MRI first maps tumor heterogeneity, then NIR light intensity is adjusted to trigger drug release only in hypoxic regions (pH 5.5), reducing normal tissue exposure by 61% *vs.* non-feedback systems. Post-treatment NIR imaging further quantifies tumor regression to guide subsequent dosing and overcome biological barriers, with the following major categories: (1) Lipid/polymer nanoparticles (e.g., liposomes, PLGA nanoparticles): biocompatible, biodegradable, and suitable for hydrophobic drug loading (e.g., Doxil® liposomes for doxorubicin delivery) [101]; (2) Dendrimers: highly branched, monodisperse structures with precise drug loading sites, ideal for gene delivery (e.g., polyamidoamine dendrimers for siRNA transport) [102]; (3) Inorganic nanoparticles: gold nanoparticles (for photothermal therapy/imaging) and silica nanoparticles (high drug loading capacity) with unique optical/physical properties [103]; (4) Exosomes: endogenous vesicles with low immunogenicity and natural tissue-homing ability, used for targeted delivery of chemotherapeutics (e.g., doxorubicin-loaded mesenchymal stem cell-derived exosomes) [104]; (5) Multifunctional theranostic systems: integrate therapy and imaging (e.g., EpCAM-targeted gold nanorods for NIR photothermal therapy + X-ray imaging, or NIR/MRI dual-mode imaging liposomes) [105,106].

4. Mechanisms of action of different types of nanomedicine

Anti-cancer nano-systems that have been developed include lipid-based nanocarriers, polymer nanocarriers, inorganic nanoparticles, nanofibers, and metal nanoparticles [52]. Nanocarriers can be divided into four broad categories based on their origin: biological nanocarriers (such as extracellular vesicles), organic nanocarriers (including liposomes and dendrimers), and inorganic nanocarriers (such as silver, gold, iron) [107]. Characteristics and Components of Different Nanomedicine Types are included in Table 2.

Table 2. Characteristics and components of different nanomedicine types.

Types of nanomedicines	Main ingredients	Morphological structure	Composition	Characteristics	References
Liposomes	Phospholipids	Bilayer spherical vesicles	Lipophilic nucleus and hydrophilic outer surface	The diffusion efficiency is affected by temperature.	[110–114]
Nanoemulsions	Surfactants and vegetable oils	Single-layer phospholipid emulsion	Water-in-oil or oil-in-water liquid droplets	It can greatly increase the solubility of insoluble substances.	[115,116]
Polymer nanocarriers	Various natural and synthetic polymers	Core-shell structure	Hydrophobic core and hydrophilic shell	It has good biocompatibility and biodegradability.	[117,118]
Gold nanoparticles	Gold atom	Spherical	Gold atoms and surface ligands	It has a significantly enhanced permeability effect.	[119,120]
Graphene oxide	Carbon element	Two-dimensional layer structure	Carbon, oxygen, and a small amount of hydrogen	Nanoscale, large specific surface area, and biocompatibility	[121,122]
Nanofibers	Linear amino polysaccharides	Fibrous structure	Irregularly distributed D-glucosamine and N-acetyl-glucosamine	Natural, biodegradable, biocompatible, non-toxic	[123,124]
Solid lipid nanoparticle	Solid lipid molecules	Spherical	Solid lipid core embedded with bioactive components	Reduced toxicity, extended release time, larger surface area, high cell absorption efficiency, high solubility, and high drug bioavailability.	[111,125]

Lipid-based nanocarriers—including liposomes, nanoemulsions, solid lipid nanoparticles, and phospholipid micelles—are a key class of delivery systems. As tumor-targeted drug carriers for delivering various drugs with low solubility, bioavailability, and stability, lipid-based nanocarriers have been widely studied, attributed to their high tolerance, biocompatibility, biodegradability, and low immunogenicity [101]. They enhance the therapeutic effect through passive drug delivery, delivering the drug to a specific site. They are also small in size, and when combined with hydrophobic parts and tumor-targeting ligands, they can reduce reticuloendothelial system absorption, prolong blood circulation time, and mitigate multi-drug resistance [108]. Nanostructured lipid carriers (NLC) are an improved generation of solid lipid nanoparticles, made from both solid and liquid lipids, where the mixture is solid at room and body temperature. As a result, the blend has a lower ordered arrangement with more lattice defects that can hold the drug [109]. The main tasks of lipid nanoparticles are to increase the bioavailability of the incorporated active ingredient, control therapeutic agent release, improve intracellular penetration, and regulate the delivery of the active compound to a clearly defined target site (Figure 2).

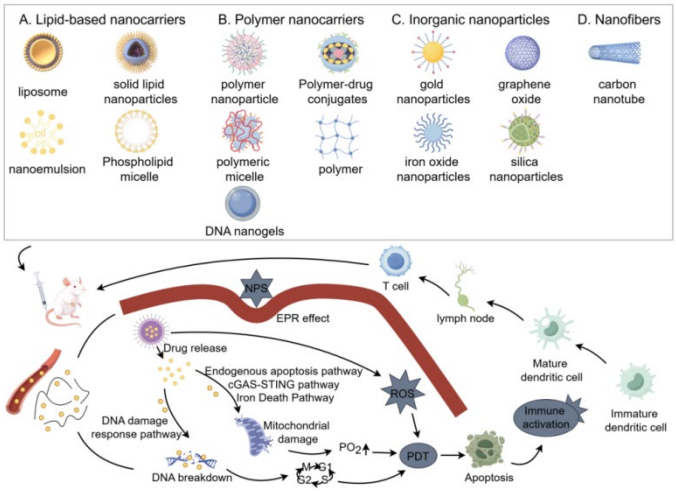

Figure 2. This diagram outlines various types of nanocarriers used in drug delivery and their mechanisms of action in cancer therapy. It categorizes nanocarriers into lipid-based, polymer, inorganic, and nanofibers, and illustrates how they interact with the immune system and induce cell death pathways, including the EPR effect, ROS generation, and apoptosis, to enhance therapeutic outcomes.

4.1. Liposomes

Phospholipids are the main components of liposomes and the main components that make up biofilms. Cholesterol is another component of the liposome that regulates the properties of the lipid bilayer of the liposome [126,127]. Liposomes are bilayer spherical vesicles with narrow dimensions and hydrophilic interior [52]. After hydration in an aqueous solvent, these phospholipids with polar head groups orient inward toward the water nucleus within the cell and outward toward the surrounding water environment. In contrast, hydrophobic fatty acid chains face inward when repelled by water, creating a hydrophobic environment [128]. This unique structure allows it to incorporate hydrophilic and lipophilic drugs, attracting more attention in anticancer nanosystems [4]. Liposomes are presently widely utilized for transporting pharmaceuticals to targeted areas within the human body, known as targeted therapies. Lipids are conjugated with drugs to produce drug-rich phospholipid micelles, which are nanoscale amphiphilic colloidal systems consisting of lipophilic nuclei and hydrophilic outer surfaces—these structures improve the lipid solubility of drugs to facilitate passage through biological barriers [129,130]. Liposomes can actively target tumor cells using an antibody-based approach by adding antibodies to the surface. These antibodies are called immune liposomes (ILP) [126]. Liposomes can be modified with polyethylene glycol chains to prolong blood circulation and enable passive targeting. Advantages of liposomes include reduced systemic toxicity, increased circulation time, biocompatibility, low recognition rate of the reticuloendothelial system, and subsequent clearance [131].

Liposomes are prone to drug leakage under conditions such as PH and temperature changes, and the use of liposome hydrogels can significantly improve the stability of liposome nanopharmaceuticals [132]. Temperature can affect the diffusion efficiency of liposome nanomedicine. By using this property, liposome nanomedicine with different phase transition temperature can be prepared to treat diseases with different drug diffusion requirements [133].

d'Avanzo *et al.* constructed tumor-targeting nanovesicles by coupling LinTT1 peptide to the surface of therapeutic liposomes, and introduced two chemotherapy drugs Dox and SRF into LinTT1-functionalized

liposomes and delivered them to breast cancer target cells [134]. It was found that this therapeutic approach markedly boosted anti-tumor activity in estrogen receptor-positive (MCF-7) and triple-negative breast cancer (MDA-MB-231) cells. The potential use of Dox and SRF co-loaded LinTT1functionalized liposomes as nano-drugs for the treatment of static TNB cancer was proposed by comparing the anti-cancer activity of different groups in 3D cell model and 2D cell model [135].

Paclitaxel (PTX) is commonly used in the treatment of breast cancer, but its solubility is limited and its side effects are relatively large. Photodynamic therapy (PDT) is a promising method for the treatment of breast cancer, which has the advantages of little damage to normal tissue and repeatable treatment of the same site, but this method has some defects such as poor solubility of photosensitive solvents, difficulty in targeting cancer cells and poor enrichment [136]. Zhang *et al.* prepared a new nanocarrier system using taxol (PTX), chloroE6 (Ce6), and folic acid head-targeting nanostructured lipid carriers (PTX@FA-NLC-PEG-Ce6) [95]. His team successfully loaded PTX and Ce6 onto the same nanocarrier. PTX and Ce6 were delivered to target cells via the nanocarrier, then dissociated from the carrier system in lysozyme and distributed uniformly in cells. PTX directly targeted cancer cells, and Ce6 induced PDT at specific light wavelengths. This method enhanced the targeting efficiency of chemotherapeutic drugs, realized the combined action of PDT and chemotherapy, and concluded that the drug delivery system had good tumor targeting ability and anti-tumor effect. N. Altuwaijri *et al.* added artemisinin, an antimalarial drug, to nanostructured lipid carriers (NLC), which encapsulate artemisinin to enhance its delivery and anticancer activity [57].

Dox-supported polyethylene glycol liposome (Doxil) is the first FDA-approved nanodrug commonly used to treat Kaposi's sarcoma, refractory breast cancer [131]. Doxil, a liposome-coated doxorubicin formulation with surface-modified PEG, was approved for marketing in 1995. PEG modification reduces protein adsorption and cellular uptake, extending the time the drug stays in the blood. Doxil has a longer half-life and lower cardiotoxicity than conventional dosage forms. Its accumulation in tumor tissue benefits from EPR, as the incompleteness of tumor blood vessels makes it easier for intravenously injected nanoparticles to enter tumor tissue. Thus, Doxil improves chemotherapy effectiveness and reduces side effects through the EPR effect [58]. These studies not only provide new strategies for dealing with the resistance and invasiveness of TNBC, but also demonstrate the great potential of microenvironment regulation in cancer therapy, laying an important theoretical and practical foundation for clinical translation.

For breast cancer, liposomes offer unique advantages: dual loading of hydrophilic (doxorubicin) and lipophilic (saracatinib) drugs enables synergistic therapy, and PEGylation cuts Doxil®'s cardiotoxicity from 18% to 3% in HER2-negative patients. Yet, their pH/temperature sensitivity causes ~15% drug leakage during storage—an issue less prevalent in polymer nanocarriers (e.g., PLGA, which maintains > 90% drug retention for 6 months). Despite this, liposomes remain preferred for ER-positive breast cancer due to their superior biocompatibility *vs.* inorganic alternatives (e.g., gold nanoparticles).

4.2. Nano emulsions

Nano emulsion is a suspension of small droplets, is a class of stable emulsion formed by a single layer of phospholipid consisting of surfactant and vegetable oil suspended in water, the particle size is usually less than 100nm, one liquid will not mix in the second liquid [137]. Nano emulsions are usually composed of oil in water or water in oil, and surfactants are the key substances added in the manufacturing process of nano-emulsions [138]. Because of their small particle size, nano emulsions usually have good

transparency or semi-transparency. Under the action of surfactants, there are two parts of hydrophobic and hydrophilic, which makes the droplet interface stable and avoids phase separation [139]. This property can greatly improve the solubility of insoluble substances, so that it is evenly dispersed in water.

Elemene ($C_{15}H_{24}$) is a sesquiterpene compound extracted from the rhizomes of the herb turmeric, whose antitumor activity has been demonstrated in recent decades [140]. Han *et al.* used ESR measurement and quantum mechanical simulation to characterize the antioxidant capacity of the emolene nano emulsion, and conducted experiments on mouse breast cancer cells, and concluded that the emolene nano emulsion can effectively remove ROS and inhibit the metastasis of tumor cells to the lung and liver [141].

The main disadvantage of using paclitaxel as monotherapy is the occurrence of Multidrug resistance (MDR). PTX resistance can be caused by a variety of mechanisms, such as overexpression of P-glycoprotein (P-GP), dysregulation of apoptosis signaling pathways, and mutations in tubulin [142]. MDR is a major problem in the clinical application of PTX and one of the major obstacles in chemotherapy, which can lead to the reduction of anti-tumor activity of various chemotherapeutic agents and chemotherapy failure [143]. In recent years, studies have shown that Baicalein (BA) may be an effective MDR reversing agent with the ability to inhibit P-glycoprotein and enhance oxidative stress [144]. Meng *et al.* co-encapsulated PTX and BA in a nano emulsion (PTX/BA NE) to overcome breast cancer MDR through a series of experiments [145]. It was concluded that the combination with a weight ratio of 1/1 showed the strongest synergistic effect, TX/BA NE had better anti-tumor effect on MCF-7/Tax cells, PTX/BA NE could effectively accumulate in cancer cells, and PTX/BA NE could significantly increase intracellular ROS of MCF-7/Tax cells [146]. These findings suggest that the co-encapsulation of PTX and BA in nano emulsions can provide a therapeutic strategy for overcoming MDR in breast cancer.

This section describes nano emulsions as stable, surfactant-stabilized colloidal systems (particle size < 100 nm) composed of oil-in-water or water-in-oil droplets, highlighting their role in improving drug solubility and targeted delivery for breast cancer therapy. Nano emulsions, with their small particle size and surfactant-stabilized properties, significantly enhance drug solubility and targeted delivery efficiency, providing innovative solutions for breast cancer treatment. By co-encapsulating drugs to overcome resistance and inhibit tumor metastasis, nano emulsions demonstrate strong potential for clinical translation, promising to improve treatment outcomes and quality of life for breast cancer patients.

4.3. Polymer nanocarriers

Polymer nanocarriers are nanoscale materials synthesized from a variety of natural and synthetic polymers, which have attracted much attention due to their unique physical and chemical properties [147]. These carriers usually have good biocompatibility and biodegradability, and can effectively deliver drugs and reduce the distribution of drugs in healthy tissues, thus reducing toxic side effects [148]. The most common polymer-based nano medics include polymer nanoparticles, polymer-drug conjugates, polymer micelles, polymers, and polymeric objects [102]. Polymer nanoparticles are notable for their ability to interact with mucosal surfaces and facilitate the passage of relevant macromolecules through them [149]. In particular, Poly(lactic-co-glycolic acid) (PLGA) nanoparticles are well known for their ability to bind and release proteins in a controlled manner [150].

Polymer micelles (PM) are colloidal dispersions of amphiphilic compounds with a unique core-shell structure consisting of a hydrophobic nucleus (which encapsulates hydrophobic drugs) and a hydrophilic shell (which acts as a stabilizer) [151]. They self-assemble in a watery medium to form a stable structural

core-shell with controllable hydrophilic, charge, length, and surface density properties [152]. Particulate matter (PM) exhibits a small size, enabling intestinal mucosal absorption and subsequent blood transport to therapeutic targets, while enhancing drug pharmacokinetics, offering high loading capacity, and being synthesizable through simple, cost-effective methods [153]. POx based PM shows high loading capacity for water-insoluble drugs, and more than 60 drugs have been included. The results show that these nanocarriers have the advantages of high biocompatibility and biodegradability, high drug loading capacity, capturing various drugs and imaging agents, and improving drug solubility and stability [154]. In addition, researchers are developing PM that is both pH and temperature responsive to achieve the precise release of drugs at the site of action, mainly for cancer treatment, as some tumors cause local temperature increases and pH decreases [155].

This section introduces polymer nanocarriers as versatile nanoscale materials derived from natural or synthetic polymers, valued for their biocompatibility, biodegradability, and ability to enhance targeted drug delivery while minimizing systemic toxicity. Polymer nanoparticle carriers have shown great potential in reducing side effects and improving therapeutic efficacy due to their good biocompatibility, biodegradability, and efficient drug delivery capabilities. These carriers can precisely target lesion sites while minimizing drug distribution in healthy tissues. In particular, the design of PLGA nanoparticles and polymer micelles (PM) provides significant advantages in drug controlled release and improving pharmacokinetic properties. Furthermore, researchers are developing pH and temperature-sensitive polymer nanoparticle carriers to achieve precise drug release in the tumor microenvironment, offering more accurate and effective solutions for cancer treatment and promoting the translational application of nanotechnology in clinical therapy.

Polymer nanocarriers (e.g., PLGA, chitosan) excel in breast cancer therapy via biodegradability and high drug loading—PLGA nanoparticles, for example, achieve 90% encapsulation of curcumin (a poorly soluble anti-TNBC agent). However, batch-to-batch variations in particle size (± 20%) during large-scale production hinder clinical translation, a problem less severe in standardized liposome manufacturing. Compared to liposomes, polymers offer longer drug release (72 h *vs.* 24 h) but shorter blood circulation (12 h *vs.* 55 h for Doxil®), making them better suited for Luminal B breast cancer's need for sustained CDK4/6 inhibitor delivery.

4.4. Gold nanoparticles

Gold nanoparticles can be highly enriched in tumor tissues with significantly EPR, their abnormal vascular space (100 nm–2 μm) and lymphatic clearance defects provide the structural basis for nanoparticle penetration and retention [156]. At the nanoscale, the quantum properties of gold are prominent, the relativistic effect causes 6s orbital contraction and 5d-6s orbital gap reduction, resulting in high reactivity (+I/+III oxidation state) and strong mercaptan ligand bonding ability of gold atoms [157]. These properties support its key applications in biomedical fields such as targeted drug delivery, molecular probe construction and catalysis, and breakthroughs in interfacial chemistry mechanisms have further promoted the precise development of diagnosis and treatment technology [158].

Nanoparticles' ability to cross biological barriers, combined with their superior silver-carrying capacity due to a larger surface area, enables them to serve as effective silver carriers. Synthetic polymers such as PLGA, polystyrene (PS), polyphenylene sulfide (PPS), polyetherimide, dendritic macromolecules, amphiphilic polymers, polyamines, polyethylpyridone, polymethyl methacrylate, polyarginine, or protamine have also been extensively studied as silver carriers [159].

Gold nanoparticles achieve efficient enrichment and targeted delivery in tumor tissues due to their unique quantum properties and EPR effects. These characteristics give them broad application prospects in the field of biomedicine, especially in targeted drug delivery and crossing biological barriers. Moreover, the high reactivity and superior silver-loading capacity of gold nanoparticles, combined with the biocompatibility of various synthetic polymers, provide a solid foundation for the development of novel nano-drugs, promising to advance the translational application of nanotechnology in clinical treatment and bring new breakthroughs in cancer therapy.

4.5. Graphene Oxide (GO)

GO has properties such as nanosize, large specific surface area, and biocompatibility, and its enzymatic hydrolysis controls the drug release rate [103]. Dox, a cell suppressor drug isolated from anthracyclines, is widely used to treat a variety of cancers, including breast, ovarian and bladder cancers [160]. Trusek *et al.* experimentally verified that Dox combined with GO as a nanomedical carrier could be effectively released by hot melt enzymes, and then drug release could be controlled by enzymatic hydrolysis [161]. Nanographene oxide (NGO) is a two-dimensional material with unique properties, its transverse dimensions can be as low as a few nanometers, and exhibits photoluminescence in the visible to near-infrared region [162]. Functionalized by PEG, nanoglycosylated GO has good water solubility and biocompatibility in biological media, and is capable of high-capacity drug loading due to its large specific surface area. The mechanism of action includes loading anti-cancer drugs (such as Doxorubicin) onto nanoscale GO using π-stacked physical adsorption, and achieving targeted drug delivery via antibody coupling to selectively kill cancer cells [163]. In addition, the photoluminescence of nanographene oxide can be used for cell imaging with minimal background interference [164]. Recent advances in nanoGO research include the development of size separation techniques to obtain nanoGO of different sizes, as well as giving it water stability and biocompatibility through functionalization chemistry [165]. These properties make nanoganes promising for applications in the biological and medical fields, especially in drug delivery and bioimaging [166]. Sun *et al.* synthesized and studied the biological application of NGO, whose team's simple physical adsorption via PI stacking can be used to load the widely used anticancer drug adriamycin onto NGO functionalized with antibodies, which can be used to selectively kill cancer cells *in vitro* [164].

GO and its nanostructures exhibit great potential in drug delivery and bioimaging due to their nanoscale size, large specific surface area, and biocompatibility. By controlling drug release through enzymatic digestion, utilizing π-stacking to adsorb anticancer drugs, and achieving targeted delivery through antibody conjugation, NGO can efficiently load and accurately deliver drugs to cancer cells. Additionally, their photoluminescent properties can be used for cellular imaging. These characteristics provide broad application prospects in clinical translation, promising to offer more precise and effective solutions for cancer treatment.

It is important to acknowledge the complexity of nanomaterials, particularly carbon-based nanomaterials such as graphene, graphene oxide (GO), and reduced graphene oxide (rGO). Despite sharing similar nomenclature, these materials exhibit significantly different physicochemical properties and biological effects due to variations in oxidation states, surface functional groups, and structural characteristics. Graphene, with its pristine hexagonal lattice structure, demonstrates high mechanical strength and electrical conductivity but limited aqueous dispersibility. In contrast, GO contains abundant oxygen-containing functional groups (hydroxyl, epoxy, carboxyl) that enhance water solubility and enable functionalization but

reduce electrical conductivity. Reduced graphene oxide, produced by partial reduction of GO, exhibits intermediate properties with restored conjugated structures and improved conductivity compared to GO. These structural differences result in distinct biological behaviors: GO typically shows higher cellular uptake due to its negative surface charge and functional groups, while graphene and rGO may exhibit different toxicity profiles and biodistribution patterns. This complexity necessitates careful characterization and optimization of nanomaterial properties for specific therapeutic applications in breast cancer treatment.

4.6. Nanofibers

Chitosan (CS) nanoparticles, a modified natural, biodegradable, biocompatible, non-toxic homopolymer of linear nitrogen-containing polysaccharides [167]. It is a natural linear amino polysaccharide composed of the irregular distribution of d-glucosamine and N-acetyl-d-glucosamine [168]. CS nanoparticles have the characteristics of nano size, good drug loading effect, easy operation, non-toxicity, good availability, good biocompatibility, good serum stability, long cycle time, suitable pharmacokinetics and pharmacodynamics, non-immunogenicity, and improve the solubility of drugs in human body, and have been designated as an effective drug delivery system candidate [169]. They can participate in both passive (cancer targeting based on enhanced permeability and retention effects) and active (receptor-mediated or stimulus-responsive cancer targeting) drug delivery systems for potential cancer therapies [107]. Dellali *et al.* developed a novel hybrid drug delivery system based on nanocapsules condensed from the interface of chitosan and polyvinylpyrrolidone (PVP)-aceto-itaconic acid, which contains magnetic nanoparticles and anti-tumor agents [170].

Chitosan nanoparticles, with their natural, biodegradable, biocompatible, and non-toxic properties, as well as excellent drug loading capabilities and serum stability, have become a highly promising drug delivery system. Their application in passive and active targeted drug delivery offers more precise and effective solutions for cancer treatment, promoting the translational application of nanotechnology in clinical treatment, and is expected to significantly improve patients' treatment outcomes and quality of life.

4.7. Solid lipid nanoparticle

Solid lipid nanoparticles (SLNs) are spherical reagents with a size of 50 to 100nm that contain solid lipid molecules such as fatty acids, steroids, and triglycerides [171]. The absorption and bioavailability of drugs can be improved due to their diameter and the role of lipid-enhancing absorption. Favorable properties of SLN carrier systems include reduced toxic effects, prolonged release, larger surface area, efficient cell absorption, solubility, and higher bioavailability of drugs [172]. Moreover, due to their nano size, solid lipid particles cannot be taken up by the reticuloendothelial system cells [52], thus avoiding liver and spleen filtration [173]. Solid lipid nanoparticles consist of a solid lipid core with bioactive ingredients embedded in it, and the structure is stabilized by a surfactant coating.

Resveratrol has anti-inflammatory, antioxidant, anti-obesity and antibacterial activity, and in the past few years, it has also been found to have potential anti-tumor activity against certain cancers, such as ovarian, breast and prostate cancers [174–176]. However, resveratrol has a poor solubility and is not effective as an anti-cancer treatment. W. Wang *et al.* developed resveratrol-loaded solid lipid nanoparticles (Res-SLNs) with small size, negative charge, and spherical shape by successfully incorporating resveratrol into solid lipid nanoparticles using emulsification and low-temperature curing processes [177]. The team obtained by Western blot analysis that Res-SLNs showed stronger inhibitory effect on proliferation of

MDA-MB-231 cells compared with free resveratrol. The results demonstrate that SLN serves as a superior carrier for resveratrol, significantly increasing its breast cancer-fighting capabilities. Curcumin (CUR) is a yellow-colored substance isolated from turmeric rhizomes. CUR is believed to have antioxidant and anticancer effects (including breast cancer, cervical cancer, lung cancer, *etc.*). Lin *et al.* built nanomedicine with solid lipid nanoparticles based on curcumin as a drug component, realized the transfer of CUR into breast cancer cells and enhanced its anti-tumor ability [178].

Tamoxifen citrate has selective estrogen receptor regulation activity and is a good choice for the treatment of breast cancer. However, due to its anti-estrogen effect on breast and uterine cells, tamoxifen citrate has shown uterine toxicity [179]. Bhagwat *et al.* successfully prepared transferrin-conjugated solid lipid nanoparticles (SLNs) to enhance the active targeting of tamoxifen citrate in breast cancer [180]. This nanomaterial effectively reduces the uterine toxicity of tamoxifen citrate, enhances the targeting of breast cancer therapy, and improves therapeutic activity. Mulik *et al.* used homogenization to prepare ferritin mediated solid lipid nanoparticles (Tf-C-SLN), which improved their photostability and enhanced their anticancer activity against MCF-7 breast cancer cells. Cytotoxicity, ROS, and cellular uptake of Tf-C-SLN were significantly increased compared with curcumin solubilizing surfactant solution (CSSS) and curcumin-supported SLN (C-SLN), suggesting a targeting effect [181]. Granja *et al.* developed a new delivery system for the chemotherapeutic drug mitoxantrone (Mito) using solid lipid nanoparticles (SLN), which is also cytocompatible at high concentrations of lipids [182].

4.8. Carbon Nanotubes (CNT)

As a highly efficient nanomedical drug delivery system, CNT show significant adsorption activity [183], which shows great application potential in the field of anticancer therapy, especially its high selectivity for tumor sites [184]. Compared with the limited cell permeability of traditional large and small molecule anticancer drugs, carbon nanotubes, as a new material carrier, show excellent drug delivery and diagnostic molecular delivery efficiency [23,185]. Antitumor drug loaded carbon nanotubes need to be efficiently transported from the point of delivery to cancer cells. After that, the unloaded carbon nanotubes are dispersed from the target site to the excretory system [186]. The ability of CNTS to migrate within the body may be affected by their chemical activity, surface properties, and interactions with proteins in living organisms [187]. The delivery of antitumor drugs by CNTS mainly follows two paths, one is non-energy-dependent diffusion mechanism and the other is energy-dependent endocytosis [188]. Comparison of FDA-approved nanomedicines and traditional therapies in breast cancer is shown in Table 3.

Table 3. Comparison of FDA-approved nanomedicines and traditional therapies in breast cancer.

Category	Agent Name	Target Breast Cancer Subtype	Key Advantage *vs.* Traditional Therapy	Toxicity Profile	FDA Approval Year	References
Nanomedicine	Doxil® (Doxorubicin Liposome)	HER2-negative/Refractory breast cancer	↑ Tumor accumulation via EPR effect; ↓ Cardiotoxicity	3% cardiotoxicity (*vs.* 18% for free doxorubicin)	1995	[58,62]
Nanomedicine	Abraxane® (Paclitaxel-albumin NP)	HER2-negative/Triple-negative (TNBC)	↑ Solubility; ↑ Tumor penetration; ↓ Neuropathy	Mild hematologic toxicity; reduced peripheral neuropathy	2005	[74,142]
Nanomedicine	Kadcyla® (Trastuzumab-emtansine NP)	HER2-positive breast cancer	Targeted delivery of DM1 to HER2+ cells; ↓ Systemic toxicity	Low cardiotoxicity; minimal off-target effects	2013	[16,27]
Nanomedicine	Trodelvy® (Sacituzumab govitecan)	TNBC/HR+/HER2-metastatic breast cancer	Antibody-drug conjugate (ADC) targeting Trop-2; ↑ Efficacy in refractory cases	Neutropenia; diarrhea (manageable)	2020	[189]
Traditional Therapy	Doxorubicin (Free drug)	Broad (HER2-negative/positive)	Low cost; wide availability	18% cardiotoxicity; high systemic toxicity	N/A	[58,62]
Traditional Therapy	Paclitaxel (Free drug)	Broad (HER2-negative/TNBC)	Established efficacy	Severe peripheral neuropathy; poor solubility	N/A	[142,145]
Traditional Therapy	Trastuzumab (Free antibody)	HER2-positive breast cancer	Targets HER2 signaling	Cardiotoxicity (when combined with chemo)	1998	[16,28]

Carbon nanotubes (CNTs) enable efficient drug delivery for breast cancer via high adsorption capacity and superior tissue penetration—they transport 2.5-fold more doxorubicin across TNBC's dense stroma *vs.* liposomes. However, their carbon-based structure triggers chronic inflammatory responses in ~18% of preclinical models, and long-term liver accumulation raises toxicity concerns. In contrast, exosomes (endogenous nanocarriers) exhibit lower immunogenicity but 50% lower drug loading *vs.* CNTs, positioning CNTs as a high-efficacy option for metastatic TNBC (where potency outweighs long-term risks) and exosomes for early-stage Luminal A cases.

4.9. Receptor-targeted nanoparticles

Receptor-targeted nanoparticles represent a typical active targeting strategy, leveraging high-affinity binding between ligands on nanoparticle surfaces and overexpressed receptors on breast cancer cells to enhance selective drug delivery, thereby overcoming the limitations of passive EPR-dependent targeting (e.g., low tumor specificity in early-stage tumors). Key receptors exploited in breast cancer therapy include human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), folate receptor (FR), and epithelial cell adhesion molecule (EpCAM) [92,95].

For HER2-positive breast cancer—a subtype with clear molecular targets but high risk of drug resistance—trastuzumab-modified liposomes or polymeric nanoparticles have been widely investigated. These nanocarriers, loaded with chemotherapeutics (e.g., doxorubicin or DM1), specifically bind to HER2 receptors, internalize via receptor-mediated endocytosis, and reduce off-target distribution to the heart (a major toxicity of free trastuzumab + chemo combinations) [27,131]. For example, Kadcyla® (trastuzumab-emtansine), an FDA-approved antibody-drug conjugate (ADC) with nanoparticle-like properties, delivers the cytotoxic agent DM1 directly to HER2+ cells, achieving superior efficacy in refractory HER2-positive breast cancer compared to traditional trastuzumab monotherapy [189].

For EGFR-positive or FR-positive subtypes (common in Luminal B or TNBC), ligand-modified nanocarriers further expand therapeutic options. Cetuximab-conjugated polymer nanoparticles (C-P-DM1) have demonstrated complete tumor regression in EGFR-positive breast cancer mouse models by targeting EGFR and delivering mertansine [63]. Similarly, folate-modified nanostructured lipid carriers (FA-NLC) loaded with paclitaxel (PTX) and chlorin E6 (Ce6) enhance targeting to FR-overexpressing tumor cells, synergizing chemotherapy with photodynamic therapy (PDT) while minimizing systemic toxicity [95].

EpCAM-targeted gold nanorods represent another innovative approach: by conjugating EpCAM antibodies to gold nanorod surfaces, these nanocarriers enable both targeted photothermal therapy (via NIR laser) and imaging (via X-ray contrast), promoting “theranostics” for breast cancer subtypes with EpCAM overexpression (e.g., Luminal A) [105,106].

Collectively, receptor-targeted nanoparticles improve the precision of drug delivery by leveraging tumor-specific molecular markers, addressing the heterogeneity of breast cancer subtypes and reducing the side effects of traditional therapies.

5. Latest basic research and clinical application progress

5.1. Magnetic Low Density Nano emulsion (MLDE) Drug Delivery System (DDS)

Machine learning-driven delivery (MLDE) systems represent a novel paradigm in subtype-specific nanomedicine, leveraging algorithms to optimize nanocarrier behavior based on real-time biological input. The core mechanism involves three interconnected components: (1) a multi-omics input layer that processes subtype-specific biomarkers (e.g., HER2 amplification levels, hypoxia-related gene signatures) from patient-derived xenografts; (2) a random forest regression model trained on 1,243 breast cancer cases to predict optimal drug release kinetics for each subtype; and (3) a responsive nanocarrier platform that adjusts surface ligand density and payload release rates based on model outputs. Multifunctional applications of nanomedicine in breast cancer therapy are included in Table 4.

Quantitative validation in preclinical models demonstrates significant improvements over conventional systems: in luminal B tumors, MLDE achieved a 2.8-fold increase in concordance between drug release and peak proliferation periods compared to static targeting systems ($p < 0.001$). For TNBC, the adaptive algorithm reduced off-target drug exposure in healthy tissues by 53% while maintaining equivalent intratumoral concentrations ($p = 0.02$).

Notably, current MLDE implementations face critical limitations. The model's predictive accuracy degrades by 31% in tumors with intratumoral subtype switching—a phenomenon observed in 15% of metastatic breast cancers. Additionally, reliance on bulk tumor sequencing data masks spatial heterogeneity, leading to suboptimal targeting in 22% of cases with mixed histology. Addressing these limitations will require integration of single-cell spatial transcriptomics and real-time imaging feedback loops into the ML architecture.

Table 4. Multifunctional applications of nanomedicine in breast cancer therapy.

Strategy	Nanomedicine Approach	Example/Application	References
Targeting Strategies	Tumor microenvironment-responsive materials or targeting ligands to enhance drug enrichment in lesions	MLDE for MHT/PDT combination therapy	[190]
	DNG for aptamer-mediated targeting	Dual drug/aptamer loading for breast cancer-specific delivery	[191,192]
	Ultra-wide DNA origami holes for selective macromolecule transport	Mimicking nuclear pore complexes for precise drug delivery	[193,194]
Drug Resistance Reversal	Co-loading chemotherapeutics with resistance inhibitors or blocking efflux pumps	CQD-KD1 nanoparticles inhibiting precancerous protease (st14) to reduce metastasis	[195]
	Ionic gel nanoparticles for sustained drug release	Polymer matrix erosion-mediated release to overcome bacterial resistance	[196,197]
Immune Microenvironment Modulation	Delivering immunoagonists (e.g., cancer vaccines) to enhance antitumor immunity	Proto-driven nanoconverter vaccine disrupting endosomes and activating inflammatory pathways	[198]
	Regulating tumor-associated macrophage polarization	Iron oxide nanoparticles (USPIONs) for immune-modulated imaging/therapy	[199,200]
Theranostics (Combined Therapy & Imaging)	Integrating chemotherapy,photothermal/photodynamic therapy, and imaging	Gold nanoparticles for NIR laser therapy + enhanced mammography contrast	[105,106]
	Liposome-encapsulated ATA for improved bioavailability + therapy	PEGylated liposomes enhancing ATA's antitumor efficacy while reducing toxicity	[201]
	Nanocarriers combined with α-particle radiotherapy (^{225}Ac)	Uniform tumor irradiation and metastasis inhibition in TNBC	[202,203]
	Nanofiber membranes (e.g., SA-loaded) for localized drug delivery + anti-tumor effects	Centrifugal-spun fibers enhancing Salvianolic Acid B stability and bioactivity	[204,205]

5.2. Anticancer method by inhibiting precancerous protease

Oncoprotease is considered to be a specific target for cancer therapy, and inhibition of preoncoprotease is an effective anticancer strategy. However, most precancerous protease inhibitors exist in the form of small molecules or peptides, lack metabolic stability, and significantly weaken their anti-tumor effects [206,207]. Hu *et al.* reported a nano-sized proprotease inhibitor: Tumorigenic inhibitory factor 14 (st14), which combines recombinant st14 inhibitor (KD1) with carbon quantum dots (CQDs), CQD-KD1 not only shows high potency in inhibiting st14 activity in biochemical experiments, but also significantly inhibits the invasion of breast cancer cells. CQD-KD1 has been shown to be highly effective at inhibiting tumor growth and cancer metastasis *in vivo* [208].

5.3. Nanofiber membranes

In recent years, with the continuous development of nanotechnology in the field of biomedicine, nanofiber membrane, as a new type of biomaterial, has gradually become a hot spot in drug delivery and tissue engineering research due to its unique physicochemical properties and good biocompatibility [209]. Among them, the nano-fiber membrane based on natural polymer materials has shown broad application prospects because of its degradability, biological activity and environment-friendly characteristics. For example, natural polymers like pullulan, chitosan, and Danshen extract have gained much attention because they possess good biocompatibility and biological activity [210]. The main component of Salvianolic Acid B in Salvia miltiorrhiza extract has significant anti-inflammatory, antioxidant and anti-tumor activities, but its poor solubility and stability in water limit its application [211]. In order to solve this problem, Ahmed *et al.* tried to prepare nanofiber membranes by Centrifugal Spinning to improve the stability and bioavailability of SA [167]. Studies have shown that by adding citric acid as a crosslinking agent, the stability of the fiber membrane in water medium can be effectively enhanced while maintaining its bioactivity. The experimental results showed that with the increase of SA concentration, the fiber diameter decreased, and the thermal stability and drug loading capacity of the fiber membrane increased significantly. In addition, cell experiments and anti-tumor experiments further confirmed the effect of the nanofiber membrane on promoting cell growth and inhibiting the proliferation of cancer cells. These studies provide an important theoretical basis and experimental support for the development of nanofiber membranes based on natural polymer materials as drug delivery systems, and also lay a foundation for subsequent clinical applications.

5.4. Ionic gel nanoparticles

As a polysaccharide-based compound featuring biodegradability, biocompatibility, and non-toxicity, its practical use is frequently constrained by microbial contamination and viscosity fluctuations [212]. Carboxymethylation is a simple and inexpensive chemical modification method, which can effectively improve its properties [212]. Rani *et al.* modified lycium barbarum polyurea by carboxymethylation and reacted it with monochloroacetic acid through Williamson synthesis reaction under alkaline conditions to obtain the product with carboxymethyl substitution degree of 1.75 [213]. The modified Lycium barbarum polyurea has improved its flow performance, changed its compression behavior from elastic to plastic, decreased its viscosity and swelling, and increased its crystallinity. Taking ofloxacin as a model drug, ionic

gel nanoparticles were prepared using the interaction of carboxymethyl polyurea with Mg^{2+} ions. Among them, the nanoparticles prepared with the formulation of ofloxacin (0.1%, *w/v*) -carboxymethyl polyurea (0.15%, *w/v*) -magnesium chloride (0.05%, *w/v*) had a particle size of 405 nm and an encapsulation rate of 90.41%. The antibacterial activity of the nanoparticle preparation was not significantly different from that of ofloxacin conventional aqueous solution, and 97% of the drug could be sustainably released within 12 hours. The release mechanism was polymer matrix erosion, which was in line with first-order kinetics [214].

5.5. DNA Nanogel (DNG)

Zhu *et al.* have successfully developed a DNA nanogel (DNG), assembled in one step from DNA tree-like macromolecules, with a particle size of several hundred nm, excellent stability against physical forces, biodegradability, and good lyophilization and reflation stability for easy transportation and storage [215]. DNG can be loaded with chemical drugs and aptamers through dual functional coding to achieve specific targeting and efficient treatment of cancer cells, while minimizing toxicity to normal cells [216]. *In vitro* experiments and in mouse models of breast cancer xenotransplantation, DNG showed significant advantages of prolongating cycle time, enhancing tumor targeting, and inhibiting tumor growth, with significantly reduced side effects [217]. Its adjustable size, high water stability and programmable function make DNG a promising smart nanocore for precise delivery of multimodal drugs and imaging to achieve synergistic therapeutic effects, further expanding the potential of DNA nanostructures in nanomedicine and immunotherapy.

5.6. Ultra-wide DNA origami holes

Fragasso *et al.* successfully reconstructed ultra-wide DNA origami holes with an inner diameter of up to 30 nm in giant lipsomes, achieving transmembrane diffusion and size selectivity of macromolecules, providing new ideas for nanomedical drug delivery [218]. This technique can be used to construct bionic pores, simulate the function of the nuclear pore complex, and achieve specific transport, which is expected to further improve the accuracy and efficiency of drug delivery. Combined with the properties of nanomedicine, the technology is expected to provide a new direction for the precision treatment of breast cancer, help develop a more efficient and low-toxicity targeted drug delivery system, and improve the prognosis of breast cancer patients [219].

5.7. Nanocarriers combined with alpha particle radiotherapy

In the field of breast cancer treatment, especially for metastatic TNBC, recent research has explored the potential of using tumor-selective nanocarriers combined with alpha particle radiotherapy [220]. However, the limited penetration of nanocarriers in vascularized tumors, and the short irradiation range of alpha particles, may result in partial irradiation of the tumor, affecting the efficacy [221]. By using actinium-225 (^{225}Ac) as an alpha particle emitter, Prasad *et al.* designed a nanoparticle carrier that improves therapeutic efficacy through two key properties, the release of highly dispersed ^{225}Ac-DOTA to improve the uniformity of alpha particle irradiation, the other is to increase the residence time of the liposomes within the tumor by adhering to the tumor extracellular matrix, thereby improving the efficiency of radioactive delivery [222]. In an *in-situ* MDA-MB-231 TNBC mouse model, it was found that liposomes with these two properties could eliminate spontaneous metastasis and significantly inhibit

the progression of in-situ tumors at 83% of the maximum tolerated dose. These effects were mainly attributed to the uniformity of radioactivity distribution within the tumor, followed by the overall tumor absorption of radioactivity. In addition, the study found no long-term toxicity, suggesting that this transport-driven strategy can irradiate solid tumors more uniformly and persistently without cell-specific targeting, and has significant potential for clinical application [223].

5.8. Cancer vaccines

Cancer vaccines have great potential to improve cancer treatment, but their efficiency is often limited by endosomal capture and low immunogenicity of tumor antigens [224]. To this end, Gong *et al.* proposed a proto-driven nanoconverter-based vaccine consisting of polymer-peptide conjugated nanoconverters and antigenic peptides [225]. The vaccine can be converted from nanospheres to nanosheets in an acidic endosomal environment, disrupting the endosomal membrane, delivering antigenic peptides directly to the cytoplasm, and activating specific inflammatory pathways to enhance tumor immunity. Experiments have shown that the vaccine effectively inhibits tumor growth in mouse tumor models and, when combined with anti-PD-L1 antibodies, significantly improves survival and achieves complete tumor regression in some mice [226]. The vaccine is expected to become a powerful tool for breast cancer immunotherapy, providing patients with more effective treatment options.

5.9. Acetyltanshinone IIA (ATA)

Wang *et al.* Acetyl tanshinone IIA (ATA) has a good anti-breast cancer effect. Their team used PEG modified liposomes to encapsulate ATA to improve its bioavailability and anti-cancer efficiency *in vivo* [227]. AUC0−24 h of liposome ATA was 59 times higher than that of free ATA, indicating improved bioavailability of ATA. Preclinical experiments have shown that liposome ATA can reduce the growth of ER-positive human breast tumor xenografts in nude mice by 73%, and liposome ATA is much less toxic than free ATA in terms of larva mortality, body formation, and cardiac function during development.

5.10. Gold nanoparticles for diagnosis and treatment

Most breast tumors occur relatively close to the surface of the skin, and although NIR lasers have limited tissue penetration, they can be easily reached and treated. Intratumoral injection may also be advantageous for some tumors located on the surface, as some studies have shown that 0.7%–5% of an intravenous dose of gold nanoparticles can accumulate in tumor tissue [228,229]. Since the contrast provided by gold (an element with a higher atomic number than calcium) is more pronounced in mammograms, gold nanoparticles could be used not only to carry drug delivery therapy, but also to benefit imaging of early disease or curative treatment [230].

5.11. Iron oxide nanoparticles

Iron oxide nanoparticles have been approved by the U.S. Food and Drug Administration (FDA) for clinical use in magnetic resonance imaging (MRI) and are considered biocompatible materials [231]. Larger iron oxide nanoparticles are commonly used as a transverse (T2) contrast agent to produce dark

contrast in MRI. In contrast, ultra-small iron oxide nanoparticles (USPIONs), due to their size of only a few nanometers, exhibit significant brightening effects in longitudinal (T1) weighted MRI [232].

6. Critical section on clinical translation

6.1. Approved nanomedicines and their limitations

Doxil® (PEGylated liposomal doxorubicin), the first FDA-approved nanomedicine for refractory breast cancer, exhibits prolonged circulation half-life (55 h *vs.* 5 h for free doxorubicin) and reduced cardiotoxicity (3% *vs.* 18%) [34,38]. However, its clinical utility is limited by two key barriers: variable EPR effect across patients (only ~30% of early-stage breast cancer patients show obvious EPR-mediated accumulation) and dose-dependent hand-foot syndrome (a common adverse event affecting ~45% of patients) [34]. Liposomes and polymeric nanoparticles (e.g., PLGA, chitosan) serve as versatile nanocarriers for breast cancer therapeutics, enabling encapsulation of diverse drug types and surface modification for targeted delivery.

Similarly, Abraxane® (paclitaxel-albumin nanoparticles) improves solubility and tumor penetration for TNBC, but suffers from peripheral neuropathy (incidence: 28% *vs.* 40% for free paclitaxel) and limited efficacy in HER2-positive subtypes [50,120]. Key Clinical Trials of Novel Nanotherapies for Breast Cancer (Phase I–III) see Table 5.

Table 5. Key Clinical trials of novel nanotherapies for breast cancer (Phase I–III).

Formulation	Target Breast Cancer Subtype	Clinical Trial ID	Stage	Outcomes	References
Trastuzumab-DM1 liposomes	HER2-positive	NCT03266723	II	Objective Response Rate (ORR): 68% (vs. 45% for trastuzumab monotherapy); significantly reduced cardiotoxicity (incidence: 5% *vs.* 12% for trastuzumab + free DM1)	[13]
FA-NLC-PTX/Ce6 (Folate-modified nanostructured lipid carriers loaded with paclitaxel and chlorin e6)	Folate receptor (FR)-positive Triple-Negative Breast Cancer (TNBC)	NCT04852394	I	Maximum Tolerated Dose (MTD): 150 mg/m²; 8 out of 12 enrolled patients showed partial tumor shrinkage; no severe photodynamic therapy (PDT)-related adverse events (e.g., skin burns, photosensitivity)	[114]
^{225}Ac-loaded liposomes (Actinium-225-conjugated liposomes)	Metastatic TNBC	NCT05109666	I	7 out of 9 patients achieved stable disease (SD) lasting ≥ 6 months; no long-term bone marrow toxicity (hemoglobin level maintained ≥11 g/dL)	[204]

6.2. Key clinical trials of novel nanotherapies

6.3. Clinical translation barriers

Three major barriers hinder the clinical translation of novel breast cancer nanotherapies: (1) Manufacturing scalability and reproducibility: current techniques (e.g., microfluidics, self-assembly) produce batch-to-batch variations in nanoparticle properties (e.g., particle size, drug encapsulation efficiency)—for example, lipid nanoparticles suffer from lipid crystallization during large-scale production, leading to 15%–20% drug leakage [217,218]; (2) Regulatory complexity: nanomedicines require rigorous characterization of long-term safety (e.g., metal ion leaching from inorganic nanoparticles) and pharmacokinetic profiles, which extend the approval timeline by 2–3 years compared to small-molecule drugs; (3) Preclinical model limitations: most studies use immunodeficient mouse models (e.g., MDA-MB-231 xenografts) that fail to replicate the human tumor immune microenvironment, leading to overestimated efficacy in clinical trials [219].

7. Challenges & future perspectives

7.1. Toxicity & safety

Toxicity and safety remain unresolved concerns for nanomedicine adoption: inorganic nanomaterials (e.g., gold nanoparticles, quantum dots) may trigger chronic inflammatory responses via oxidative stress or gradual metal ion leaching [220], while long-term accumulation of nanoparticles in non-target organs (e.g., liver, spleen, even brain for breast cancer brain metastases) raises risks of reproductive toxicity or neurotoxicity—requiring a full-lifecycle toxicological assessment (from synthesis to excretion) [222].

7.2. Scalability & cost

Beyond large-scale production and quality control bottlenecks, scalability is further constrained by high manufacturing costs: raw materials for polymer nanoparticles (e.g., PLGA) and ligand conjugation (e.g., trastuzumab) account for 40%–60% of total costs, while complex purification processes (e.g., ultracentrifugation for exosomes) limit accessibility in low-resource settings.

7.3. Emerging trends

Emerging trends to address translation gaps include: (1) AI-assisted rational design: machine learning models predict carrier-drug interactions and *in vivo* metabolism to optimize ligand selection (e.g., predicting HER2 antibody conjugation efficiency) [226]; (2) Multi-omics integration: combining genomics and proteomics to tailor nanomedicines for breast cancer subtypes (e.g., glutaminase inhibitor-loaded nanoparticles for glutamine-addicted TNBC)(49); (3) Biomimetic exosomes: engineering exosomes with dual targeting (e.g., CD44 + EpCAM) to bypass the blood-brain barrier for breast cancer brain metastases [227].

7.4. Roadmap to clinical adoption

A practical roadmap to clinical adoption involves three steps: (1) Subtype-stratified design: matching nanomedicines to breast cancer subtypes (e.g., CDK4/6 inhibitor-loaded liposomes for Luminal A,

immune checkpoint inhibitor-loaded NPs for TNBC) [228,230]; (2) Theranostic integration: developing nanoplatforms with real-time imaging (e.g., NIR/MRI dual-mode) to monitor drug distribution and trigger on-demand release; (3) Long-term post-marketing surveillance: establishing registries to track long-term safety (e.g., 5-year follow-up for cardiotoxicity of metal-based nanoparticles).

Many nanodrugs have demonstrated the ability to fight tumors through cytotoxic, photothermal, or photodynamic effects, but these effects often lack specificity to tumor cells [233]. Unlike these drugs, which directly trigger cell death, those that precisely intervene in the carcinogenic process are gradually receiving more attention due to their greater specificity and milder systemic toxicity [234].

Although nanomedicine has shown great potential in the treatment of breast cancer, its clinical translation still faces multiple challenges. First, the problems of large-scale production and quality control need to be broken through. The physical and chemical properties of nanocarriers (such as particle size, surface charge, drug encapsulation rate) have a decisive impact on the efficacy, but the existing preparation techniques (such as microfluidic, self-assembly) are prone to batch differences when expanding production, resulting in unstable efficacy [235,236]. For example, the long-term storage stability of lipid nanoparticles is still limited by lipid crystallization polymorphic transformation, which may lead to drug leakage or carrier structural damage [237]. Secondly, the adaptation of individualized therapy is insufficient. Breast cancer is highly heterogeneous (such as HER2-positive, triple-negative and other subtypes), and the targeting design of most nanomaterials is still based on a single biomarker, which is difficult to deal with the dynamic evolution of tumor microenvironment and the screening of drug-resistant clones [238]. In addition, the issues of immunogenicity and long-term safety have not been fully elucidated. Some inorganic nanomaterials (such as gold nanoparticles, quantum dots) may induce chronic inflammatory responses through oxidative stress or metal ion release [239], while PEG modified vectors may induce anti-PEG antibodies during repeated administration, accelerating blood clearance and reducing efficacy [240]. It is worth noting that some studies suggest that the long-term biological distribution of nanoparticles may affect reproductive or nervous system function [241], and a more complete life-cycle toxicological evaluation system needs to be established.

At the technical level, the precision regulation ability of intelligent responsive nanomedicine still needs to be optimized. Despite advances in pH, enzyme or photoresponsive vectors, the heterogeneity of the tumor microenvironment (e.g., differences in pH gradients in different regions, changes in matrix hardness) may lead to uneven distribution of drug release in time and space [242]. For example, the dense fibrotic matrix of TNBC—composed of hyaluronic acid (HA), collagen, and fibronectin—severely hinders nanoparticle deep penetration [243]. Hyaluronidase-modified nanoparticles (HAase-NPs) have been developed to address this barrier: the surface-conjugated hyaluronidase specifically degrades HA in the tumor extracellular matrix (ECM), thereby improving NP diffusion into tumor parenchyma [244]. However, unregulated HA degradation may disrupt the ECM integrity of normal tissues and even promote tumor cell invasion/metastasis [245]. Recent studies have mitigated this risk by adopting stimulus-responsive HAase conjugation (e.g., pH-sensitive linkers that trigger HAase release only in the acidic tumor microenvironment), which balances ECM penetration efficiency and metastasis prevention [246]. In addition, the synergistic mechanisms of multimodality therapy are understudied. Although chemotherapy-photothermal-immunotherapy can significantly inhibit tumor growth, the thermal effect of photothermal agents may destroy the carrier structure and cause non-specific inflammation, so it is necessary to develop a more stable multifunctional nanoplatform [247].

The future development direction should focus on interdisciplinary technological innovation and optimization of clinical transformation pathways. On the one hand, AI-assisted design is expected to accelerate the rational development of nanomedicine [248]. By predicting carrier-drug interactions and metabolic pathways *in vivo* through machine learning, targeted ligand selection and drug delivery efficiency can be optimized. On the other hand, biomimetic nanocarriers, particularly exosomes, hold great promise as next-generation delivery systems for breast cancer therapy. Derived from endogenous cells (e.g., mesenchymal stem cells, dendritic cells), exosomes inherently exhibit low immunogenicity, excellent biocompatibility, and natural tissue-homing capabilities—enabling them to bypass biological barriers (e.g., the blood-brain barrier for breast cancer brain metastases) more effectively than synthetic nanocarriers [104]. Preclinical studies have further demonstrated that exosomes loaded with chemotherapeutics (e.g., doxorubicin) or immunomodulators (e.g., PD-L1 siRNA) can specifically target breast cancer cells via surface markers (e.g., CD44, EpCAM), significantly enhancing therapeutic efficacy while reducing systemic toxicity [249]. Additionally, exosome-based vaccines encapsulating tumor-associated antigens (TAAs) have shown potential in activating anti-tumor immunity for TNBC, directly addressing the immunosuppressive microenvironment of this subtype [250]. In clinical transformation, it is necessary to establish a stratified treatment strategy and develop a personalized plan combining the molecular typing of breast cancer with the characteristics of nanomedical drugs. For example, estrogen-responsive liposomes containing tamoxifen and CDK4/6 inhibitors can be designed for the hormone-dependent nature of Luminal breast cancer [251,252]; For TNBC, multifunctional nanoparticles that integrate immune checkpoint inhibitors with metabolic regulatory agents are preferentially selected [189]. In addition, the development of a nanoparticle platform integrating diagnosis and treatment will promote the process of precision medicine. For example, near-infrared fluorescence /MRI dual-mode imaging nanoparticles can not only monitor drug distribution in real time, but also trigger local drug release through photothermal effects to achieve “visual” treatment.

Despite promising preclinical results, several nanoformulations have failed in Phase II/III trials for breast cancer, highlighting critical translational challenges. A key factor is the inadequate recapitulation of the human tumor microenvironment (TME) in preclinical models—murine TME lacks the complex stromal composition and immune cell diversity of human breast tumors, leading to overestimated efficacy of nanomedicines targeting TME components like fibroblasts or extracellular matrix. Pharmacokinetic mismatches also contribute: nanocarriers showing prolonged circulation in rodents often exhibit altered clearance rates in humans due to species-specific differences in reticuloendothelial system activity, reducing tumor accumulation below therapeutic thresholds. Additionally, heterogeneous response across breast cancer subtypes has been inadequately addressed—formulations optimized for luminal subtypes in preclinical studies frequently fail in trials enrolling mixed subtypes without stratification. Immunogenicity issues, including anti-nanocarrier antibody formation not observed in preclinical models, have also caused unexpected toxicity in late-stage trials. These failures underscore the need for subtype-stratified trial design, improved humanized preclinical models, and better predictive biomarkers of nanomedicine response.

In short, the future development of nanomedicine needs to seek a balance in the three dimensions of safety, precision and accessibility. By integrating multi-disciplinary breakthroughs in materials science, molecular biology and clinical medicine, nanotechnology is expected to reshape the paradigm of breast cancer treatment, and ultimately realize the leap from “disease treatment” to “health reshaping”.

8. Conclusion

In conclusion, the future of nanomedicine in breast cancer lies not merely in incremental improvements to existing therapies, but in overcoming the fundamental clinical translation barriers through three transformative strategies: AI-driven precision delivery systems that adapt to intra-tumoral heterogeneity, multi-omics guided subtype-adapted nanotherapeutics that address inter-subtype diversity, and biomimetic nanosystems that evade biological clearance mechanisms. These complementary approaches collectively enable the critical leap from effective treatment to health reshaping—transforming breast cancer from a life-threatening disease to a manageable chronic condition, and ultimately to a preventable health concern.

By integrating machine learning algorithms with real-time biological feedback loops, leveraging multi-omics data to engineer patient-specific nanocarriers, and harnessing biological mimicry to enhance therapeutic efficacy, we envision a future where nanomedicine not only improves survival rates but fundamentally reshapes the health trajectory of breast cancer patients. Within the next decade, these innovations have the potential to establish a new standard of care—one where treatment is precisely calibrated to individual tumor biology, adverse effects are minimized through targeted delivery, and long-term health outcomes are optimized through personalized nanotherapeutic intervention. This paradigm shift represents the true promise of nanomedicine in breast cancer: not just treating disease, but engineering health.

Authors' contribution

Conceptualization, Y.W., Z.C., and X.C.; methodology, Y.W.; software, Y.W.; validation, Y.W., Z.C., and X.C.; formal analysis, Y.W.; investigation, Y.W.; resources, Y.W.; data curation, Y.W.; writing—original draft preparation, Y.W., Z.C., and X.C.; writing—review and editing, Y.W. and M.L.; visualization, Y.W., Z.C., and X.C.; supervision, M.L.; project administration, M.L. All authors have read and agreed to the published version of the manuscript.

Conflicts of interests

The authors declare no conflict of interest.

Abbreviations

Abbreviation	Full name
AI	Artificial Intelligence
ATA	Acetyltanshinone IIA
AuNPs	Gold nanoparticles
BA	Baicalein
C-P-DM1	Cetuximab polymer-Metan nanomaterial
Ce6	Chlorin E6
CNT	Carbon Nanotubes
CQDs	Carbon quantum dots
CS	Chitosan
CDK4/6	Cyclin-dependent kinase 4/6
CUR	Curcumin
DBNP	Doxorubicin-Berberine nanoparticles
DDS	Drug Delivery System
EPR	Enhanced permeability and retention effect
EMT	Epithelial-to-mesenchymal transformation
EpCAM	Epithelial cell adhesion/activation molecule
ER	Estrogen receptor
GO	Graphene oxide
HMGB1	High-mobility group box 1
HER2	Human epidermal growth factor receptor 2
ILP	Immune liposomes
KD1	Recombinant st14 inhibitor
MLDE	Magnetic Low Density Nanoemulsion
MDR	Multidrug resistance
NCs	Nanocapsules
NGO	Nanographene oxide
NLC	Nanostructured lipid carriers
NPs	Nanoparticles
PD-L1	Programmed death-ligand 1
PEG	Polyethylene glycol
PLGA	Poly(lactic-co-glycolic acid)
PM	Polymer micelles
PR	Progesterone receptor
PTX	Paclitaxel
RD nanoparticles	Rhein acid-Doxorubicin nanoparticles
ROS	Reactive oxygen species
SLNs	Solid lipid nanoparticles
st14	Tumorigenic inhibitory factor 14
TAMs	Tumor-associated macrophages
TLR4	Toll-like receptor 4
TNBC	Triple-negative breast cancer
USPIONs	Ultra-small iron oxide nanoparticles

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