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Advanced Nanoparticles Drug Delivery Techniques for Enhanced Solubility in BreastCancer Treatment

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Abstract
Breast cancer remains the leading cause of death among women worldwide. Traditional chemotherapy is often limited by poor drug solubility, systemic toxicity, and nonspecific targeting, leading to significant side effects. Nanoparticle-based drug delivery systems offer promising alternatives to traditional chemotherapy, improving solubility and target specificity. This paper explores how nanoparticles could transform breast cancer therapy and its pathogenesis. The pathophysiological complexity of breast cancer, including genetic and molecular changes driving tumor development and metastases, presents novel approaches to these problems. Nanoparticle-based drug delivery methods offer two main approaches: active and passive targeting. Active targeting involves functionalizing nanoparticles with ligands or antibodies that bind to receptors overexpressed on cancer cells, improving drug delivery accuracy. Nanoparticle-based drug delivery methods offer benefits such as regulated and prolonged drug release, enhanced solubility and bioavailability of hydrophobic drugs, and reduced negative effects. Potential applications include liposomes, dendrimers, and polymeric nanoparticles in preclinical and clinical environments. However, challenges such as regulatory obstacles, potential toxicity, and mass production complexity hinder their clinical application. The study concludes with future projections indicating the potential for further innovation in drug delivery techniques to address issues with poorly soluble drugs.

Keywords: Breast cancer, Drug delivery systems, Nanoparticles, Lipid-based carriers, poorly soluble drugs, Traditional chemotherapy

1. Introduction

Still a complicated disease, breast cancer (BC) requires continuous research and development to improve survival rates and quality of life. With estimated over two million new cases and about five million deaths (2014), it is the most common disease having great mortality among women worldwide according to the International Agency for Research on disease (IARC). Despite great progress in detection and treatment, this is the most deadly cancer [1, 2]. Primary source of BC in a breast is the terminal duct of lobule unit with epithelial cells lining. One might classify this cancer cells as non-invasive or in situ (in the same location) [3]. Invasive BC is the term used when the cancer cell spreading outside of the basement membrane of the lobules and ducts into surrounding normal tissues. Among the several forms of BC are ductal carcinoma, lobular carcinoma, and inflammatory mammary cancer [4]. Several stages of breast cancer are categorized using the Tumor, Node, Metastasis (TNM) classification. Early stages of invasive carcinoma are TNM stage I, TNM stage II, TNM stage IIIA, and most of these tumors are regarded operable historically. **Fig.** 1 shows the several phases of BC. Over 90% of BC diagnosis are detected early and could possibly be treated with systemic, radiation, and surgical treatments, 5 year survival rates for early BC patients undergoing suitable treatment are more than 75% [5]. In recent years, the BC patients have less curable choices for treatment. Emerging novel delivery systems might provide an appropriate approach for early detection and possible therapy. Cancer research nowadays concentrates on enhancing BC treatment with different chemotherapeutic agent delivery strategies. Among these novel drug delivery systems are nanoformulations [6], liposomes [7], hydrogels [8], exosomes [9], dendrimers [10], microspheres [11], microbubbles [12], phytosomes [13], and micelles [14]. Through enhancing solubility and bioavailability and enabling exact targeting of cancer cells with less impact on healthy tissues, nanoparticles present exciting developments in breast cancer treatment. Since the first liposome image in 1964 [15] over half a century, FDA has approved over 50 nanoparticles-based treatments [16]. Undoubtedly, after decades when doxorubicin liposomes and paclitaxel-albumin nanoparticles entered the market, nanoparticles open a new category of drug delivery and bring it into a new height [17]. After that, efforts were directed on pushing the nanoparticles-based therapy into research and development and great attention was paid to it. In general, these nanomedicines were basic carriers; liposomes, for example, were nanocapsules that helped drug distribution be more effective and increase tolerance. Apart from that, the main pharmaceuticals given by

nanomedicines were antibiotics and anticancer agents [18]. Nanomedicines have demonstrated potential target capability to improve efficacy and reduce negative impact by the natural affinity and selective binding of desired ligands. Many ligands with greater active targeting capabilities have been utilised, including endogenous folic acid and hyaluronic acid [19–21], however, the effectiveness is not sufficient. This may be attributed to competitive inhibition, inactivation of designed ligands, and corona coating [22–24]. These traits are becoming increasingly important in order to maximise nanomedicine's active targeting effect [25]. Based on a so-called increased permeability and retention (EPR) effect, which comes from specific leakage of aberrant neovascularisation in tumour, nanomedicines have been produced with the potential of targeting delivery for solid tumours [26]. Considered as positive targeted delivery without ligands, the EPR effect causes nanomedicines to aggregate more in the tumor area as the blood arteries in normal tissue are intact. There were ideas challenging the EPR effect, nevertheless, and claiming that nanomedicines' trans-vascular action is dose- and receptor-dependent active transport [27, 28]. Investigations remain necessary for determining the truth. Furthermore, during the last 10 years, drug delivery nanoparticles have made considerable advances in the development of well-designed and intelligent drug delivery systems to overcome difficult challenges in the treatment of intolerant diseases. Nanoparticles are distinct, complex in composition, and versatile in use. In a solid tumor, the tumor tissue is usually thick, and hypoxia occurs in the inner region, resulting in apoptosis, an acidic environment, and abnormal production of stress proteins, which are typical traits of the tumor microenvironment [29–31]. Tumor grows quickly and loses control. Novel nanoparticles have been developed to fit and exploit the tumor microenvironment, for example, using linkage with acidic response for drug payload realizes specific drug release in tumor [32], degradation by overexpressed enzyme shrinks nanoparticles size for deep tumor penetration [33] and increasing size enhances tumor retention [34]. Not only are these smart drug delivery systems carriers addressing drug concerns, but they also greatly improve the potential of medications in therapy and allow drugs with hitherto unattainable capabilities via drug optimization. Although the classification and delivery technique of nanoparticles are not newly developed, many outstanding works have been reported in these fields in recent years; hence, a systematic and thorough review is needed to summarize these works to show the frontiers and directions in drug delivery nanoparticles.

This review delves into breast cancer pathophysiology and nanoparticle drug delivery systems,

covering unique strategies, advantages, benefits, applications, advanced techniques, targeted strategies, and efficacy. It focuses on ongoing research to increase patient survival rates and quality of life, challenges, and future opportunities.

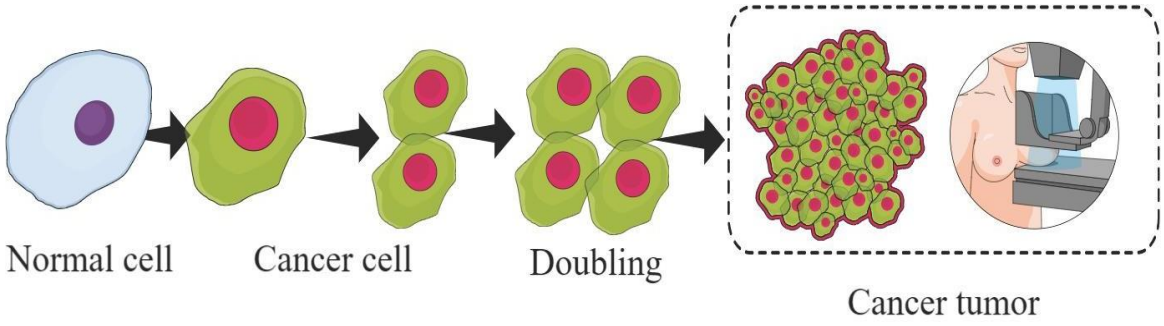

Fig. 1 Different stages of breast cancer

2. Pathophysiology of breast cancer

Breast cancer is a form of proliferative carcinoma that develops from breast tissue [35]. The shape alterations, dimpling of the skin, nipple leakage are indications of the BC [36]. Spread-related symptoms could include discolouration [37] and swelling of breast tissue accompanied by a lump connected with pain. Among the proliferative breast lesions are sclerosing adenosis, ductal hyperplasia, fibroadenomas and intraductal papillomas [38]. Hydroxyl radicles generate lesions and generate cancer etiology in ductal carcinoma [39]. According to BC's epidemiology, stimulation of estrogen in the absence of cyclic progesterone secretion causes breast cancer as estrogen receptor alpha is essential for the development of breast cells. Breastfeeding's preventive impact assists in reducing the quantity of sex hormones associated with cancer by depleting the probability of BC [40]. Cancer originating in lobules, ducts, skin, and molecular point of view including estrogen receptor-negative tumors and enriched human epidermal growth factor receptor (EGFR) 2 forms structural classification of BC. Among the positive tumor subtypes for estrogen receptors are luminal A and luminal B tumors [41]. The kind of BC can be ascertained depending on the receptor (progesterone, estrogen) on the cell nucleus and over-expression [42]. Breast cancer is rather frequent among women Hormonal, environmental, personal, and genetic risk factors define elements behind cancer [38]. Woo et al. propose that by

reducing EGFR expression, antimutagenic drugs have triggered cell death in MCF7 BC cells, Protein degradation is the reason behind down-regulation of EGFR [43]. According to Franco et al., changed expression of the several gene isoforms might lead to carcinogenesis and gene isoforms necessary for epithelial formation underdeveloped. According to recent studies, altered gene isoform expression plays a significant role in BC development [44]. **Fig.** 2 shows the cellular morphology of breast cancer.

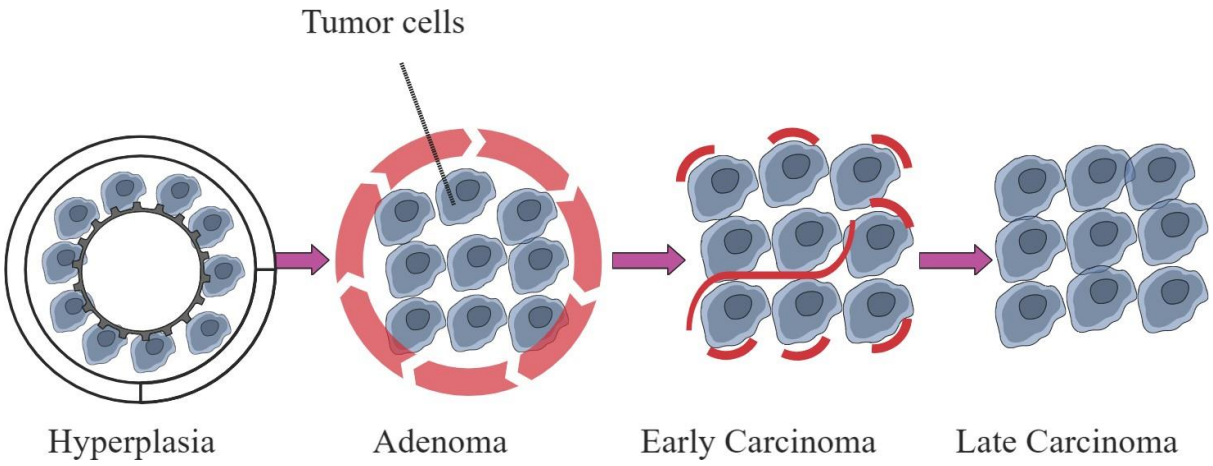

Fig. 2 Cellular morphology of breast cancer

3. Nanoparticles Drug Delivery

Nanotechnology has been widely used in cancer treatment; nanoparticles are a key instrument for drug delivery. Among other benefits, these systems provide advantages including solubility, stability, biocompatibility, and precise targeting [45]. Nanoparticles have been found to inhibit cancer-related drug resistance by targeting efflux transporter overexpression, defective apoptotic pathways, and hypoxic circumstances [46]. Usually comprised of ions, either inorganic or organic molecules, nanoparticles are minuscule crystals with dimension less than 100 nm i.e., restricted to nanoscale in all three dimensions with a surrounding integral interfacial layer. Their great scientific relevance is in nanomedicine, in which drug transport and activity are improved by means of nanoparticles. Typical small size and unique coating of nanoparticles helps to transport hydrophobic anticancer drugs to exact places in the body with lower opsonization by

immune system. Especially targeting metastasized breast cancers, a lot of nanoparticles comprising gold, silica, fullerene, quantum dots, carbon nanotubes and magnetic nanoparticles have been developed [47, 48]. The advantages of nanoparticles-based delivery systems are improved biocompatibility, multifunctional encapsulation of active compounds, less degradation during blood circulation, passive or active targeting, effective administration and minimal negative effects [49]. Carbon nanotubes, fullerenes, graphene, and nanodiamond based nanostructured materials are main carbon based nanosystems under development for cancer theranostics [50, 51].

Since three factors greatly affect the effectiveness of the nano-drug delivery and hence regulate therapeutic success, the NPs employed in medical therapy usually have specified sizes, shapes, and surface properties [52]. In general, NPs with a 10 to 100 nm diameter range are fit for cancer treatment since they can efficiently carry medications and get improved permeability and retention (EPR) function. While particles bigger than 100 nm are probably eliminated from circulation by phagocytes [54], smaller particles can readily leak from the normal vasculature (less than 1–2 nm) to damage normal cells and can be quickly filtered by kidneys [53]. Furthermore affecting the bioavailability and half-life of NPs are their surface properties. NPs coated in hydrophilic materials, such polyethylene glycol (PEG), for example reduce opsonization and thereby prevent immune system clearance [55]. Therefore, NPs are usually changed to become hydrophilic, which increases the time period of drugs in circulation and improves their penetration and accumulation in tumors [56, 57, 55]. The several properties of nanoparticles define their therapeutic impact in the treatment of cancer. **Fig.** 3 shows several types of NPs for BC cancer treatment.

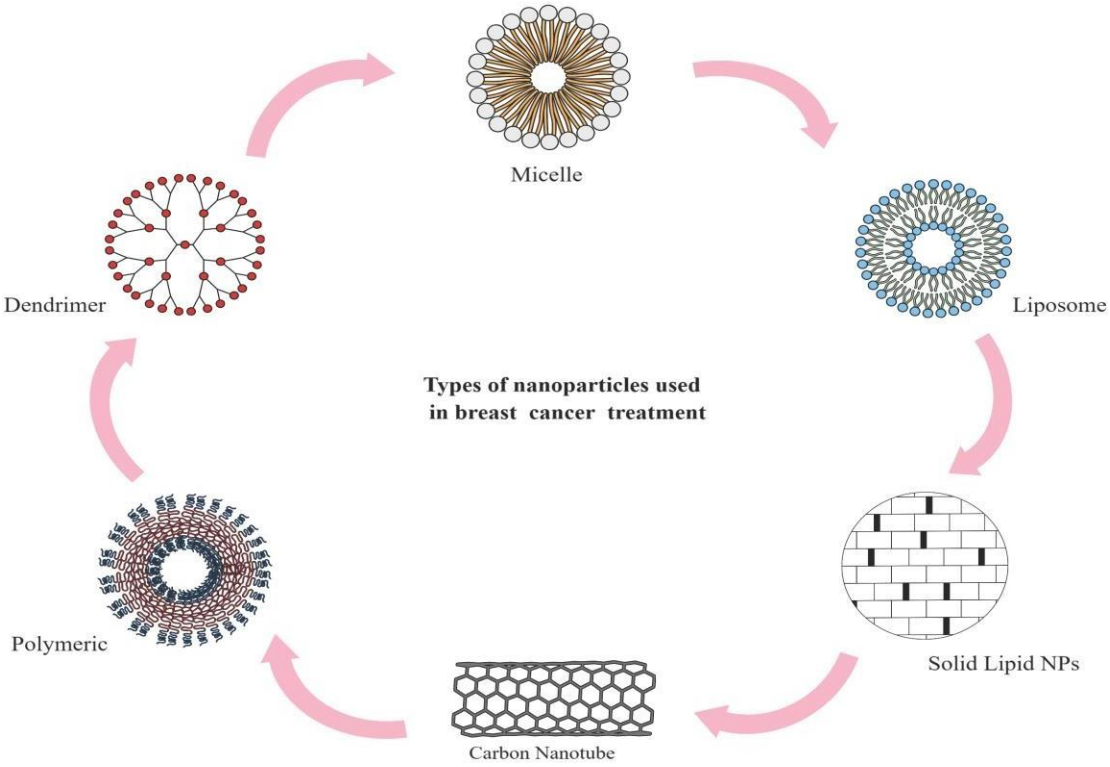

Fig. 3 Several types of nanoparticles used in breast cancer treatment

4. Novel strategies of nanotechnology- based BC treatment:

Targeting cancer cells especially is an essential characteristic of nano-carriers for drug delivery since it increases the therapeutic effectiveness and protects normal cells from damage. Targeting design of NP-based drugs has been investigated in many studies. First understanding tumor biology and the interaction between nano-carriers and tumor cells will help one to better handle the difficulties of tumor targeting and the design of the nano-carriers. Two main categories might help one classify the targeting mechanisms active and passive targeting represent in **Fig.** 4.

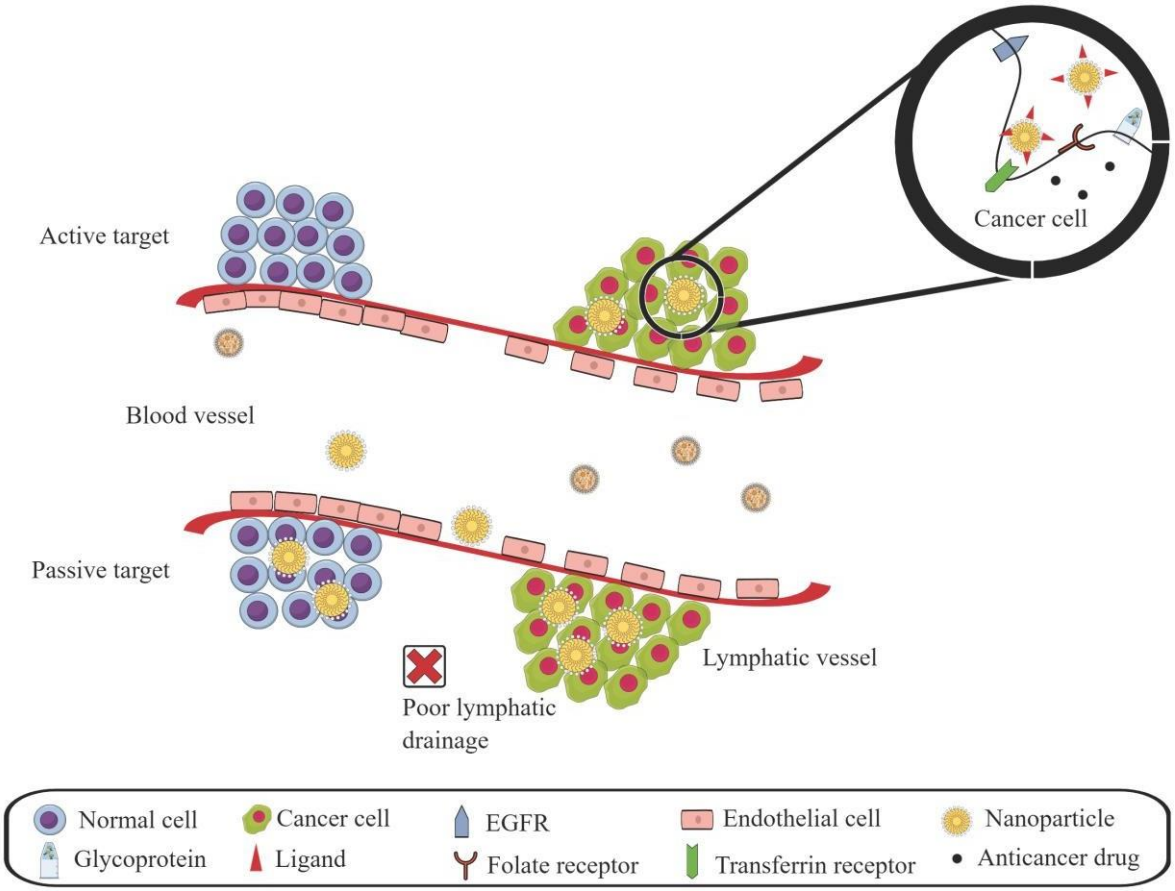

Fig. 4 Active and passive targeting of NPs to cancer cell

4.1. Passive Targeting:

Also known as EPR, this reflex (passive) targeting without any particular receptor-targets, nanocarriers may penetrate cancerously sites cells by endocytosis i.e. macropinocytosis and improve the value of drugs which act on intracellular organelles. The EPR is known to increase drug distribution especially for solid malignant carcinogens (breast cancers). The nanomedicine should have a<100 nm in diameter with hydrophilic surface to avoid in order to extend circulation in the body and improve the medication targeting effect: Macrophages cleaned the hydrophilic coating developed on nanoformulation using polyethylene glycol (PEG), polysaccharides, poloxamines [58]. As nanocarriers enter malignant cells passively and act on intracellular targets, EPR helped the anticancer impact of RNA medicines, paclitaxel, and doxorubicin to show improvement [59].Though passive targeting is not selective and effective method of drug delivery.

4.2. Active Targeting:

One interesting approach to enhance focused distribution of drugs is active targeting **Fig**. 4. This approach places certain ligands or antibodies on the surface of nanoparticles such that they interact to particular cancer cell receptors. This reduces exposure to healthy cells [60] while nevertheless enabling more exact and effective drug delivery. Developing nanoparticle-based therapies that specifically destroy cancer cells while sparing healthy tissues will help to transform cancer treatment, these treatments target cancer cells expressing certain surface receptors by utilizing antibodies, therefore enabling therapeutic chemicals to reach the tumor location [61]. This method might not be successful, though, for tumors that lack specific surface receptors targeted by the nanoparticles, therefore restricting drug delivery and reducing efficacy in treating the malignancy. More study is being done to maximize this clinical application approach. The development of nanoparticles that may simultaneously target several surface receptors is one possible option under investigation, hence boosting the possibility of properly delivering therapeutic chemicals to cancer cells [62]. To further drug distribution and raise the general effectiveness of cancer treatments, researchers are now looking at other delivery techniques including gene therapy or nanocarriers. By lowering the negative effects of chemotherapy and boosting the precision of targeted treatments, these developments in drug delivery systems could completely transform cancer treatment [63]. Furthermore, the application of nanotechnology in cancer treatment has great potential for tailored medicine since nanoparticles may be made to especially target the particular traits of different cancers. Through ongoing study and development, these creative ideas could eventually provide cancer patients with more tailored therapy choices [64].

5. Advantages of nanoparticle-based drug delivery systems:

In cancer treatment, nanoparticle-based drug delivery systems have many benefits including more effective drugs targeting and penetration into tumors cells, so increasing therapeutic efficacy [65]. However, these methods also have several drawbacks including possible toxicity issues and risks for immune system recognition and clearance. To maximize these systems and solve their constraints for safe and efficient therapeutic uses, much more study is required [66]. Targeting ligands on the surface, covering nanoparticles with biocompatible materials, and producing stimulus-responsive nanoparticles that release their payload in response to particular stimuli inside the tumor microenvironment helps one to change the surface properties of

nanoparticles [67]. Engineer nanoparticles with regulated size and shape is another method to increase their circulation time in the body and boost their capacity to pass through tumors. To further increase the general effectiveness of cancer treatment, researchers are now investigating the use of multifunctional nanoparticles that may concurrently provide therapeutic drugs, imaging agents, and targeting molecules. With more focused and effective treatments offered by research in nanomedicine, cancer treatment could be revolutionized [68]. Developed to directly target cancer cells, nanoparticles provide chemotherapy drugs, therefore lowering systemic dosages and damage to surrounding healthy tissues. In preclinical research, this strategy has demonstrated encouraging effects; finally, it could be implemented clinically to raise patient outcomes [69]. Drug resistance is still a problem, though, since cancer cells can evolve over time by mutations or activation of alternative signaling pathways. Targeting several routes concurrently, researchers are investigating combo treatments to circumvent drug resistance [70]. Furthermore, work is under progress to create nanoparticles with improved targeting capacity to especially target resistant tumor cells with drugs. These approaches have tremendous chance to overcome the obstacle of drug resistance and raise the efficiency of cancer treatments. Furthermore under investigation is immunotherapies' application to increase the body's own immune reaction against resistant cancer cells [71]. These treatments have demonstrated promising success in overcome resistance to medications and enhancing patient outcomes by using the immune system's capability. Constant study is aimed at finding biomarkers that could forecast medication resistance, so enabling more individualized treatment strategies fit to each patient.

6. Applications of nanoparticles in BC treatment

Rapid clinical translation of nanotechnology based on effective discoveries has transformed the discipline of cancer treatment [45]. Especially in cancer, fast developing nanotechnology offers pharmacological uses for diagnosis and treatment of various disorders. Targeting cancer, mostly for better diagnostics, effective drug delivery to tumor cells, or developing tailored therapy, nanotechnological innovations aim at Key challenge in cancer treatment is innovative nanotherapy, which addresses physio-biochemical features of nanoparticles for the clinical application followed by targeted nanoparticle drug delivery aimed to reduce the adverse effects of antitumor drugs with potential fall in conventional treatment expenses.

Formulations based on liposomes, polymeric nanoparticles and nanoparticle albumin-bound paclitaxel have already received US FDA approval or are now under clinical studies for several nanoparticulate-based chemotherapeutic delivery systems for BC treatment. Two US FDA approved nano-based drugs already on the market, Doxil® and Abraxane®, are significant treatment advancements since they have a special coating that evades attack by the immune system enabling targeted precise delivery of drugs to the cancer cells, so lowering the side effects associated with the current chemotherapies. Beyond traditional treatment, innovative nanotherapies targeting HER2 or TNBC and nanotherapies based on RNA interference, nanoparticle-mediated photothermal ablation, calcium phosphosilicate nanoparticles and novel NC provide multiple perspectives. Two main obstacles in the intended molecular therapies are loading concentration and encapsulation efficiency of active compounds; also, the choice of a suitable targeting moiety and producing uniform clinicalgrade nanoparticles at the industrial scale. Made of polymer-based matrix, nanoparticles are adaptable for surface functionalization, biocompatible, permeable, biodegradable, Natural polymers such chitosan and cellulose or synthetic polymers including poly (lactic-co-glycolic) acid (PLGA), polyvinyl alcohol (PVA), polyethylene glycol (PEG) are created. They exhibit [46] excellent drug loading, simple scalability, and controllable drug release pattern. PLGA reduces P-glycoprotein (P-gp) activity, so assisting in MDR reversal. Combination drug delivery for BC that is, simultaneous administration of several medications via a single platform is also making use of nanoparticles. Reportedly, this synergistic method has increased the efficacy, eliminated drug resistance, and raised patient survival rates [47]. **Table** 1 shows the applications of nanoparticles in breast cancer management.

Table 1 Applications of Nanoparticles in Breast Cancer Treatment

S.NO.	Type of Nanoparticle	Structure	Applications	References
1	**Lipid nanoparticles**	Biocompatible and biodegradable lipids, preferred over polymer nanoparticles due to	Enhance solubility, bioavailability, pharmacokinetics, absorption, skin	[108, 109]

		lower cytotoxicity and better scalability.	permeability, and ocular retention of drugs.	
2	**Liposomal NPs**	Circular vesicles made of phospholipids, can be monolamellar or multilamellar, low toxicity, and weak immunogenicity.	Entrap hydrophilic and hydrophobic drugs, protect drugs from degradation, improve bioavailability, and reduce cardiotoxicity.	[110, 111,112]
3	**Solid lipid NPs**	Solid lipid matrix containing triglycerides, lipids, fatty acids, steroids, and waxes, requires surfactants.	Targeted drug release, improve pharmacokinetics and biocompatibility, used in radiolabeled trastuzumab formulations for HER2-positive breast cancer.	[113, 114]
4	**Nanostructure lipid carriers (NLCs)**	Second-generation SLNs, mix of solid and liquid lipids, improved drug retention and loading capacity.	Enhanced permeability and uptake of drugs like tetrahydro curcumin for triple-negative breast cancer, dual-drug delivery systems for increased efficacy.	[115, 116]
5	**Polymeric NPs**	Made from natural or synthetic polymers, can encapsulate or attach drugs on the surface.	Effective for hydrophobic cancer drugs, minimal toxicity, excellent biocompatibility, and biodegradability.	[117, 118]
6	**Co-polymers**	Amphiphilic block copolymers, can load multiple drugs and regulate release.	Prevention of premature drug release, targeted delivery, and enhanced drug loading capacity.	[119, 120]
7	**Micelles**	Self-assembly of amphiphilic molecules,	Longer circulation times, reduced toxicity, and	[121, 122]

		hydrophilic heads, and hydrophobic tails.	increased tumor deposition. Used in delivery of hydrophobic cancer drugs.	
8	**Polymersomes**	Amphiphilic copolymers forming double-layer structures.	Sustained drug release, reduced diffusion into cells, superior stability. Effective for targeted delivery of drugs like camptothecin and silibinin.	[123]
9	**Homopolymers**	Polymers made from one type of monomer.	Effective drug carriers due to predictable properties.	[124]
10	**Hydrogel nanocapsules**	Three-dimensional polymeric structures, responsive to environmental changes.	Smart drug delivery systems, improved drug stability, compatibility, and targeted delivery. Used for chemo-photothermal therapy in breast cancer.	[125, 126]
11	**Dendrimers**	Spherical configuration with hyper-branched architecture	Delivery of anticancer drugs (e.g., 5-fluorouracil, camptothecin, curcumin) - Effective as chemotherapeutic agents - Enhanced intracellular uptake and accumulation of drugs	[127, 128]
12	**Inorganic NPs**	Stable, hydrophilic, biocompatible, and non-toxic	Drug/gene delivery , Stimuli-responsive release	[129]
13	**Magnetic NPs**	Consist of maghemite (Fe2O3) or magnetite (Fe3O4) with a	-MRI imaging - Hyperthermia treatment - Targeted drug delivery,	[130]

		stabilizing matrix	examples include Ferumoxides, Resovist, Ferumoxtran-10, and Clariscan	
14	**Carbon-based NPs**	Cylindrical structures like carbon nanotubes	-Delivery of anticancer drugs - Photodynamic therapy (PDT) - Enhanced solubility and biocompatibility	[131]
15	**Ceramic Nanoparticles**	Solid inorganic materials (oxides, carbides, carbonates, phosphates).	Drug delivery: High loading capacity, durability, and resistance to chemical reactions. Imaging and dye degradation.	[132]
16	**Silica NPs**	Silicon and oxygen-based compounds with a honeycomb structure.	Drug delivery High loading capacity, adjustable structure, and automated drug release. Enhanced drug loading and release efficiency under ultrasound.	[133]
17	**Titanium NPs (TiO2)**	Titanium dioxide (TiO2) possesses biocompatibility, lightweight construction, corrosion resistance, thermal stability, and low toxicity.	- Targeted drug delivery systems. - Photothermal therapy. - Reactive Oxygen Species (ROS) generation under laser irradiation. - Antineoplastic and antimicrobial properties. - Photodynamic therapy (PDT). - Conjugation with cancer drugs for enhanced	[134]

			efficacy.	
18	**Gold NPs (AuNPs)**	Core made of gold, surface-modified with cationic polymers or functional groups such as carboxyl, amine, and thiol.	- Contrast agents and dosage intensifiers. - Nanocarriers for peptides, pDNAs, proteins, siRNAs, and chemotherapy drugs. - Protection from enzymatic degradation. - Extended half-life and enhanced drug effectiveness. - Targeted drug delivery. - Photothermal therapy. - Conjugation with drugs for cancer therapy.	[135]
19	**Hybrid NPs**	Combination of organic and inorganic materials	-synergistic drug delivery, reduced drug resistance, enhanced efficacy - Tumor hypoxia reduction - Enhanced stability and circulation duration	[136]
20	**Quantum Dots (QDs)**	Semiconductor nanocrystals with size-dependent fluorescence.	Bioimaging Enhanced fluorescence for imaging cancer cells. Drug delivery: Functionalized QDs for targeted delivery and bio-imaging in TNBC. Improved biocompatibility and reduced toxicity.	[137]

7. Potential & benefits of nanoparticles in breast cancer treatment

Nanotechnology has lately become a fascinating discipline with great possibilities for developing innovative techniques of drug delivery systems for cancer treatment. Among the several benefits of using nanotechnology in medicine include increased therapeutic efficacy, tailored delivery, less adverse effects, and better patient outcomes [100]. Getting therapeutic drugs to the tumor site with minimum effect on healthy tissues is one of the main difficulties in cancer treatment. Typical constraints of conventional drug delivery systems are limited solubility, limited stability, and fast bodily evacuation. By encapsulating the therapeutic substances within nanoparticles, liposomes, or polymeric micelles [101], nanotechnology-based drug delivery systems can overcome these difficulties, nevertheless. Particularly nanoparticles have attracted a lot of interest because of their special qualities: small size, large surface area-to----volume ratio, and capacity to be functionalized with ligands under control. These characteristics allow nanoparticles to aggregate preferentially at the tumor site either actively targeting (ligand-receptor interactions) [102] or passively targeting (enhanced permeability and retention [EPR] impact). Achieving site-specific drug delivery helps nanotechnology-based systems to reduce off-target effects and raise the concentration of therapeutic compounds in the tumor, hence increasing treatment results. Moreover, by including stimuli-responsive materials into the drug delivery system, nanotechnology enables drug-controlled release, therefore guaranteeing sustained and localized drug administration. These materials release the therapeutic ingredient at the intended place by responding to particular stimuli, including pH, temperature, or enzyme activity [103].Furthermore by co-encapsulating multiple drugs or including diagnostic compounds inside the nanoparticles, nanotechnology-based drug delivery systems can help to facilitate combination therapy. This method enables synergistic effects whereby several treatment agents cooperate to maximize efficacy by reducing drug resistance [104]. Preclinical and clinical investigations for cancer treatment have revealed many nanotechnology-based drug delivery methods to be rather promising. Among the examples are polymeric nanoparticles with docetaxel (Onivyde®) and liposomal versions of paclitaxel (Abraxane®). Comparatively to their traditional equivalents, these systems have shown enhanced pharmacokinetics, lowered toxicity, and raised anticancer activity [105–107]. Overcoming the restrictions of conventional medication delivery technologies, nanotechnology has great promise to transform cancer treatment. Along with the possibility for combination therapy, the capacity to create targeted and regulated drug

release makes nanotechnology-based drug delivery systems a viable path for enhancing anticancer drugs including pharmaceuticals derived from natural ingredients.

Rapid development of cancer nanotherapeutics is driven by their implementation to address various limits of conventional drug delivery systems including nonspecific biodistribution and targeting, lack of water solubility, poor oral bioavailability, and low therapeutic indices. By means of ideal size and surface properties, nanoparticles have been developed for maximum circulation time in the bloodstream, thereby improving the biodistribution of cancer medications. Through combination of their improved permeability and retention impact and tumor microenvironment, they are also able to transport their loaded active medications to cancer cells by specifically leveraging their pathophysiology. Apart from this passive targeting method, active targeting approaches employing ligands or antibodies aimed against particular tumor targets enhance the specificity of these therapeutic nanoparticles. Using nanoparticles could help to overcome or at least minimize drug resistance, another factor compromising the effectiveness of both conventional chemotherapeutic drugs and molecularly targeted ones. As one of the primary mediators of multidrug resistance, P-glycoprotein cannot detect nanoparticles accumulating in cells, thereby increasing their intracellular concentration of medicines. Currently under active research and on their way as the next generation of nanoparticles, multifunctional and multiplex nanoparticles help to provide customized and tailored cancer treatment [72].

Emerging as a class of cancer treatments are nanoparticles particles in the size range 1–100 nm. Early clinical data point to qualities including better targeted localization in tumors and active cellular absorption that would allow nanoparticle therapies to show greater efficacy while concurrently lowering negative effects [73]. For cancer treatment, a nanoparticle-based drug delivery system (DDS) seems promising. By means of 1) increasing half-life of susceptible drugs and proteins, 2) enhancing the solubility of hydrophobic drugs, and 3) enabling regulated and targeted release of drugs in sick site [74], the nanoparticle-based DDS demonstrates increased efficacy compared with conventional DDS.

7.1. Reduced Side Effects and Enhanced Targeting:

Through precisely increasing drug accumulation within tumor cells, nanoparticles help to reduce related adverse effects like hematological and cardiotoxicities [75, 76]. Comparatively to conventional doxorubicin, liposomal doxorubicin (LD) and pegylated liposomal doxorubicin (PLD) have shown improved cardiac tolerability [75]. As improving the biodistribution of cancer

treatments, nanoparticles increase their circulation time and target specificity, hence reducing nonspecific biodistribution and targeting [72, 74]. Functionalizing nanoparticles with specific ligands allows one to maximize therapeutic efficacy and minimize off-target effects on healthy tissues while exactly recognizing and binding to cancer cells. This approach raises therapeutic efficacy and concentrates drugs at the tumor site.

7.2. Enhanced Solubility and Bioavailability:

Through utilizing enhanced surface area, nanoencapsulation, nanoemulsions, surface modification, and controlled release, nanoparticles can raise drug solubility. Their large surface area to volume ratio lets solubilization and dispersion go farther. While nanoemulsions improve solubility of hydrophobic compounds, nanoencapsulation shields therapeutic molecules from breakdown. Surface modification by ligands or hydrophilic coatings raises the affinity of nanoparticles for water molecules. Extended therapeutic effects and constant solubility made possible by controlled release these techniques improve therapeutic treatments and assist to overcome obstacles in drug distribution. By improving the solubility and bioavailability of natural substances, nanoparticle-based delivery systems enable improved transport to cancer cells and delaying of their release, therefore providing a more prolonged therapeutic effect due of their reduced metabolism and excretion [77].

7.3. Controlled and Targeted Drug Release:

Through allowing the controlled release of encapsulated compounds, nanoparticles can enhance drug solubility and therapeutic effects. Reducing fast evacuation increases solubility and bioavailability. Furthermore, certain ligands can be functionalized to enable exact targeting of cancer cells, hence enhancing treatment efficacy and lowering off-target effects [78]. Since they improve drugs solubility and bioavailability, lower side effects, and offer targeted and regulated drug release, nanoparticles show significant promise for treating breast cancer. They also provide an achievable method to get beyond drug resistance. Using nanoparticles in cancer treatment is a major advancement that might provide breast cancer patients with safer and more efficient treatment substitutes. **Table** 2 shows various nanoparticle approaches for breast cancer treatment.

Table 2 Various Nanoparticle approaches for breast cancer treatment

S.NO.	Formulation	Drug Name	Composition	Method of Preparation	Outcome	References
1	Polystyrene polysoyaoil–diethanol amine nanoparticles	Curcumin and α-tocopheryl Succinate	epigallocatechin gallate–conjugated curcumin and α-tocopheryl succinate–loaded polystyrene–polysoyaoil–diethanol amine nanoparticles	double-emulsion solvent evaporation method	effectively inhibit tumor growth and reduce toxicity	[138]
2	Solid lipid nanoparticles of tamoxifen	Tamoxifen	2.5% stearic acid, 5% Tam and 2.5% Tween 80	hot homogenization method	Tam-SLNs could potentially overcome Tam-resistance by inducing apoptosis in breast cancer.	[139]
3	Polydopamine-Functionalized CA-(PCL-ran-PLA) Nanoparticles	Docetaxel	Colic acid, D,L-Lactide (3,6-dimethyl-1,4-dioxane-2,5-dione, C6H8O4), 4-(dimethylamino)pyridine (DMAP), 1,3-diisopropylcarbodiim	facile dopamine polymerization method	It's effectively increased the local drug concentration in tumor sites,	[140]

			ide (DCC), 2-(3,4-dihydroxyphenyl) ethylamine (dopamine) hydrochloride, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT),		minimized side effects, and significantly eliminated tumors.	
4	Polymeric Micelles	Paclitaxel and Lapatinib	polylactide-co-poly(ethylene glycol) (PLA-PEG) filomicelles	co-loaded into micelles.	Therapy of HER-2-positive & HER-2-negative breast cancers	[141]
5	Amino lipid derived nanoparticles (NPs)	Paclitaxel and camptothecin	paclitaxel amino lipid (PAL) derived nanoparticles (NPs), P53 mRNA	combinational therapy	increases the cellular uptake as and decrease the tumour volume	[142]
6	chitosan based glycolipid nanaosystem	Doxorubicin	doxorubicin hydrochloride	chitosan based glycolipid-like nanocarrier	Enhanced cellular uptake and avoid drug Resistance	[143]
7	Polymer-lipid hybrid nanoparticles	Psoralen	Psoralen soy lecithin Poly (D, L-lactide-	nanoprecipitation method	Significant improved the	[144]

			co-glycolide) (PLGA, 50:50)		antitumour efficacy	
8	Gold nanoparticles hybrid nanoparticles	Curcumin Quercetin Paclitaxel	Turmeric Curcumin Quercetin Paclitaxel	green synthesis method	potential anti-cancer properties of gold nanoparticles in a combinatorial approach	[145]
9	Biological Nanoparticles	H-Ferritin	H-Ferritin nanoparticle loaded with Olaparib	pH-dependent disassembly/reassembly method	significant increase in anticancer efficacy	[146]
10	Hyaluronic Acid Derivative-Based Nanoparticles	Lapatinib	Lapatinib Sodium dodecyl sulfate Pyridine triphenyl phosphonium bromide	tumor targeting method	exhibited a better tumor growth suppression profile than the other groups after intravenous injection.	[147]

8. Challenges of nanoparticles in breast cancer treatment

Treating cancer has been transformed by immunotherapies, which target and destroy cancer cells via the immune system. Still, it's important to know how these treatments might influence a woman's likelihood of getting breast cancer [79] with investigating the long-term consequences

of immunotherapies and their influence on breast cancer risk factors, researchers want to maximize therapy approaches and guarantee patient safety. One issue is if immunotherapies might raise women's risk of breast cancer. Understanding how immunotherapies affect breast cancer risk factors would enable medical practitioners to deliver individualized treatment and guide their choice of course of action. Furthermore, knowing any correlations between immunotherapy and breast cancer risk may enable the development of plans to lower risk and enhance patient outcomes [80]. Examining the long-term impact of a certain immunotherapy treatment on breast cancer risk variables in a sample of breast cancer patients could be part of a comprehensive study. Over several years, the trial would follow patients' development, evaluate changes in their risk factors, and match them to a control group devoid of immunotherapy [81]. A thorough counterexample could be a subset of immunotherapy treatment recipients who demonstrated a drop in risk variables rather than an increase. Changes in lifestyle, genetic differences, or personal reaction to the medicine could all help to explain this. Before rendering firm findings on the impact of the medication on breast cancer risk factors, researchers should take these confusing elements into account. Further research is crucial for academics to look at the fundamental causes of the declining risk factors among some immunologically treated individuals [82]. Examining possible lifestyle modifications, genetic differences, and personal reactions to the drug helps one to have a more complete knowledge of how the drug affects breast cancer risk factors. This will help researchers to make more precise recommendations and conclusions on the application of immunotherapy in the treatment of breast cancer [83]. The immune system's capacity to either destroy nanoparticles or build them up in unexpected areas, therefore compromising their efficacy, presents major obstacles for cancer nanodrug delivery. Nanodrugs find it challenging to access and distribute via a tumour's microenvironment given their extensive extracellular matrix and aberrant blood arteries [84]. Targeting ligands onto nanoparticle surfaces that especially identify and bind to cancer cell receptors helps to overcome these challenges by means of tailored drug delivery systems. This strategy reduces off-target effects and improves therapeutic efficacy. For this aim, several targeting ligands including aptamers, peptides, and antibodies have been investigated [85]. Monoclonal antibodies developed to attach to antigens on cancer cells and coupled to nanoparticles loaded with chemotherapeutic medicines constitute antibody-targeted medication delivery. This strategy minimizes side effects [86–92], increases patient outcomes, maximizes the drug's impact on

cancer cells, and lessens damage to healthy organs. This strategy is ineffective, nevertheless, in situations where tumors show heterogeneity that is, different cells expressing differing degrees of the targeted antigen. Targeted drug delivery methods can also be less successful depending on cancer microenvironments that prevent antibodies from entering or nanoparticles from reaching the tumor.

Table 3 Nanoparticles Based Cancer Drug Therapies for BC (ongoing research in Clinical trials)

S.NO	Drug	Disease	Interventions	Clinical trial phase	Outcome	Sponsors	Study complition date	Ref.
1.	Combination with Cabozantinib or With Pembrolizumab and Nab-Paclitaxel	Solid Tumors Involving the Abdomen or Thorax	Atezolizumab, Cabozantinib S-malate, Nab-paclitaxel, Procedure: Tumor Treating Fields Therapy	Phase1	The study evaluates the safety and tolerability of TTF in combination with cabozantinib, nab-paclitaxel, and atezolizumab for advanced solid tumor patients over 2-3 years.	M.D. Anderson Cancer Center	9/1/2026	NCT05092373
2.	Radiation: Regional lymph node radiotherapy (RNI) including the axilla	Breast cancer	Procedure: Stained region Lymph Node Biopsy (SrLNB), radiation: Regional lymph	NA	The study examines the diagnosis and treatment of breast cancer-related lymphedema up to three years post-surgery, using methods like RVC and	The First Affiliated Hospital with Nanjing Medical	2026-07	NCT05939830

			node radiotherapy (RNI) including the axilla		bioelectrical impedance technology. It emphasizes the importance of understanding and managing complications to improve patient outcomes.	Universit y		
3.	MT-302 (A)	Epithelial Tumors, Malignant	Drug: MT-302 (A)	Phase1	The safety and tolerability of MT-302 will be assessed through adverse event incidence, maximum tolerated dose, pharmacokinetics, and the 10-point ICE screening tool, with the study continuing until Week 20.	Myeloid Therapeu tics	8/31/2028	NCT059 69041
4.	Superparamagnetic	Breast Cancer|Sentin	Drug: Superparamagneti	Phase2	The study evaluated Skin Discoloration Necrosis	Vastra Gotaland	7/1/2027	NCT061

	Iron Oxide	el Lymph Node	c Iron Oxide, Device: Technetium99		detection rates, adverse events, and skin discoloration effects using Magtrace 0.1 ml and dual technique, assessing node count and consistency.	Region		69072
5.	Carbon Nanoparticle-Loaded Iron	Advanced Solid Tumor	Drug: CNSI-Fe(II) 30 mg Drug: CNSI-Fe (II) 60 mg Drug: CNSI-Fe (II) 90 mg	Phase1	The Safety and Tolerability Assessment of CNSI-Fe (II) assesses the drug's safety and tolerability in advanced solid tumor patients, aiming to understand its pharmacokinetic profile and human effects.	Sichuan Enray Pharmaceutical Sciences Company	2/29/2024	NCT06048367
6.	superparamagnetic iron oxide (SPIO) nanoparticles	Breast Cancer, Breast Neoplasms|Se	Diagnostic test: delayed sLND	Phase3	The study examines SLND detection rates, node count, concordance, avoidance, malignancy,	Uppsala University	12/30/2027	NCT04722692

		ntinel Lymph Node			and malignancy rates in DCIS patients, comparing them cumulatively and by tracer type and surgery type. It also compares malignancy and nodal malignancy rates.			
7.	Nab-Paclitaxel, Durvalumab and Tremelimumab	Breast Cancer	The study involved a biopsy, biospecimen collection, drug use, imaging, and treatment with Durvalumab, Gemcitabine Hydrochloride, Nab-paclitaxel, and a personalized synthetic long peptide vaccine.	Phase2	The study will evaluate progression-free survival, adverse event incidence, clinical response rate, clinical benefit rate, and overall survival using Kaplan-Meier product limit methods and log-rank tests.	National Cancer Institute (NCI)	12/31/2024	NCT03606967

8.	Docetaxel, Nab-paclitaxel, Pertuzumab, Trastuzumab,Trastuzumab	Breast Cancer	Drug: Docetaxel, Nab-paclitaxel, Pertuzumab, Trastuzumab,Trastuzumab, Emtansine, Lumpectomy, Mastectomy, Radiation Therapy.	Phase2	The study will evaluate breast cancer patients' survival rates, distant disease-free and relapse-free survival, and grade adverse events using Kaplan-Meier and Greenwood methods up to three years post-treatment.	ECOG-ACRIN Cancer Research Group	12/31/2038	NCT04266249
9.	Radiation With or Without Aguix Gadolinium-Based Nanoparticles	Brain Tumor, Colorectal Cancer, Gastrointestinal Cancer	Radiation: Stereotactic radiation drug: AGuIX gadolinium-based nanoparticles	Phase2	The study evaluates brain metastasis recurrence in neurologic patients using tests like RANO, PFS, TTP, and Gray's test. It also measures daily activities, detection of new metastases, radiation	Dana-Farber Cancer Institute	2026-02	NCT04899908

					necrosis, seizures, steroid use, local recurrence, and neurocognitive function.			
10.	Magseed, Metallic clip and guide wire	Breast Conserving Surgery	Device: Magseed, Metallic clip and guide wire	NA	Specimen volume, The surgical specimen is weighed after removal., Perioperatively	Sahlgrenska University Hospital, Sweden	12/31/2025	NCT06463600
11.	nab-Paclitaxel+carboplatin, Paclitaxel+carboplatin	Breast Cancer	Drug: nab-Paclitaxel+carboplatin, Paclitaxel+carboplatin	Phase3	The study measures remission, tumor stem cell proportion, progression-free survival, overall survival, and adverse events in cancer treatment, with PCR indicating remission,	Shengjing Hospital	11/30/2026	NCT04137653

					immunohistochemistry indicating tumor stem cell proportion, and OS indicating overall survival.			

9. Future prospect

Despite various barriers in the way, even if great amounts of effort and resources have been used in research and development of drug delivery nanoparticles, there is still a long way to the clinical usage of these unique-designed nanoparticles. Although approximately 200 clinical studies on nanoparticles have been conducted, the main issue causing phase II and III failures in over a 100 clinical studies is low efficacy [93, 94]. The responsibility should go to the poor preclinical result, possible toxicity of nanomaterials, limited quality control and challenging production amplification of nanoparticles. The discrepancy between clinical and preclinical results from the still lacking accurate in vitro and in vivo models to assess actual patient treatment. **Table** 3 illustrates ongoing research in Clinical trials. Future preclinical studies should thus create and apply creative approaches to help evaluation, including precisely-simulated organoid, organ on the chip and patient-derived xenografts [95]. More importantly, given the low elevation and residual insufficient delivery of nanoparticles in many diseases, new delivery materials, methods and approaches are still much sought for. On the other hand, defining the mechanism of diseases and the connections between diseases and nanoparticles would greatly increase the efficacy and future research possibilities on nanoparticles. Furthermore, administered for patient, the possible toxicity of nanoparticles significantly reduces the clinical translation. The erroneous preclinical stage simulation and evaluation also help to explain this scenario. Conversely, some engineering endogenous nanoparticles also raise questions regarding immunogenicity and inescapable consequences on normal physiological processes; the exogenous materials derived nanoparticles usually do more harm to the progress [96]. Though lack of knowledge regarding toxicity always makes clinical research difficult, most researchers concentrate on the efficacy and overlook possible toxicity of nanoparticles in preclinical research. Therefore, it is critical necessity to call for further evaluations in these areas when design, optimize and develop a nanoparticle at preclinical stage. Furthermore needed are new biocompatible materials for the composition of nanoparticles and some more practical and quick ways to assess their toxicity [97]. Furthermore of great relevance is the quality control in expanding manufacture of nanoparticles. Many new and clever nanoparticles are intricate in com-position and functions, and excess in materials, which makes it difficult to guarantee the quality. Aiming to maintain functionalities the most and simplify materials to suit manufacturing needs, future nanoparticles need optimization in compositions, preparations, and efficacy. Great

compositions also have moral worth and demand investigation. Resolving these issues will greatly help to ensure the success of clinical research since there are still additional areas in which future drug delivery nanoparticles need optimization: off-target distribution, unanticipated in vivo interaction and drug disability. Finally, instead of concentrating on the efficacy, future research and development of nanoparticles should combine and maximize the composition, assessment techniques, accurate efficacy, toxicity and possible interaction. Comprehensive studies of nanoparticles are vital and important since they could help to effectively boost the clinical translation.

According to significant efforts done for effective management of BCs with least negative effects and considerable advance in the knowledge of molecular biology of BC and nanoformulations discoveries, Surprising results emerged from the literature review on nanomedicines now under evaluation for BC therapy and therapeutically applied for the same purposes. Agreement with these innovative approaches requires careful consideration even if the nanoformulation's complexity increases. Since active targeting forms the foundation of most nanotherapeutic BC treatment strategies. Active targeting is theoretically better than a passive one; integration of targeting moieties with nanocarriers results in formulation complexity that could turn into perhaps higher toxicity and immunogenicity as well, increased production expense, and good manufacturing practice problems, Same relevant with nanoformulations combining several drugs. Novel nanoformulations must be designed with enough evidence proving they are therapeutically more active, sufficiently stable, and reasonably affordable [99].

10. Conclusion

Nanotechnology offers a promising approach for direct targeting of cancer cells while reducing damage to healthy tissues. Therapeutic drugs can be carried directly to the cancer site via nanoparticles, overcoming obstacles and challenges like limited drug penetration and drug resistance. Continuous developments in nanotechnology may alter cancer treatment by allowing individualized medicine strategies tailored to specific patient requirements. Nanoparticle-based drug delivery systems represent major progress in breast cancer treatment, improving solubility and bioavailability of hydrophobic drugs. Passive and active targeting, via functionalized ligands or antibodies, reduces systemic toxicity and adverse effects. Benefits of nanoparticle-based drug delivery include lower adverse effects, larger drug concentrations at the tumor site, and controlled drug release. However, challenges such as large-scale manufacturing complexity,

potential toxicity, and rigorous regulatory criteria require ongoing research, innovation, and cooperation among medical professionals, scientists, and regulatory authorities. Future directions of nanoparticle-based drug delivery in breast cancer treatment appear promising, with more complex and efficient formulations anticipated from continuous developments in nanotechnology and better knowledge of cancer biology.

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Declarations

Research Involving Humans and Animals Statement

Not applicable.

Informed Consent

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Competing Interests

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