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**Review Article**

# Innovations In Nanotechnology and Advances in Breast Cancer Treatment

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## ABSTRACT

One of the leading causes of death for women globally is breast cancer. Surgery, chemotherapy, and radiation therapy are the three primary therapeutic approaches used to treat breast cancer, while chemotherapy is the treatment of choice for the majority of malignancies. Applications of nanotechnology in cancer treatment have garnered a lot of interest in recent years. The several forms of nanoparticles including liposomes, micelles, polymeric nanoparticles, solid lipid nanoparticles, and gold nanoparticles and their usage in the treatment of breast cancer are the main topics of this review. Nanotechnology has advanced in the last few decades and been used to treat cancer. The targeted delivery of medications for the treatment of cancer, especially breast cancer, is currently greatly aided by nanotechnology. Drugs' therapeutic efficacy can be increased and their toxicity to healthy tissues or organs reduced by using nanoparticles to target tumors and regulate the delivery of medications to specific locations. Furthermore, immune cells can be stimulated to fight malignancies by nanoparticles. As a result, nanoparticles hold promise for use in upcoming studies and treatments of cancer.

## INTRODUCTION

Currently, the most frequent cancer diagnosed worldwide is breast cancer (BC). One in nine women will have breast cancer at some point in their lives, with an estimated 2.3 million women were diagnosed with BC annually. With about 6,70,000 deaths annually, it is also the second most common cause of cancer-related mortality in women, after lung cancer. Thankfully, mortality has dropped, with 80% of patients living for five years.[1,2] A variety of cancers of the mammary glands are referred to as breast cancer (BC). It was the most prevalent neoplasm among women in 2022, according to GLOBCAN, and one of the most often diagnosed cancers globally. Based on immunohistochemical characteristics, BC exhibits significant heterogeneity and can be divided into four subtypes: triple negative breast cancer

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(TNBC), which lacks expression of any of the aforementioned receptors; human epidermal growth factor receptor positive (HER2+); progesterone receptor positive (PR+); and estrogen receptor positive (ER+). PR and ER are both prognostic and diagnostic variables. Women with an ER+ BC have a higher overall survival rate in relation to the ER, and 70–75% of invasive breast carcinomas have high expression of ER. [3-6] Because it can predict prognosis and the responsiveness to endocrine therapy, ER expression is frequently utilized to choose the best course of treatment. Higher PR levels are positively correlated with overall survival, whereas lower PR levels are typically associated with more severe forms and a worse prognosis. [7] However, even after accounting for the additional detection rate from screening, the incidence of breast cancer keeps rising. In order to detect breast cancer, invasive biopsy is performed for the histological confirmation of invasive disease after self- and clinical assessment, radiography (including MRI, mammography, and ultrasound), and radiography. [8] For the treatment of breast cancer, numerous anticancer medications, including doxorubicin, methotrexate, paclitaxel, docetaxel, and tamoxifen, have received approval. Since drug-loaded nanoparticles have a high loading capacity and are less toxic, stable, effective, specific, and tolerable than traditional chemotherapy drugs, they are regarded as a promising tool for cancer treatments. Nanotechnology has been used extensively in recent decades. [9–11] Breast cancer has been treated with a variety of treatment approaches, such as chemotherapy and radiation therapy, which prevents the tumor from growing and recurring. However, these drugs' poor target and affinity are the cause of their low therapeutic efficacy. [12] Thus, there is a need for novel and efficient techniques to identify and treat breast cancer. Nanoparticles, which vary in size from 1 to 100 nm, can interact with a wide spectrum of organelles and biomolecules. [13] These characteristics make them appropriate for a range of uses, including biomedicine and chemical reactions. Gold nanoparticles and quantum dots (QDs) are employed at the molecular level to diagnose cancer. Nanoparticle-based molecular diagnostic methods can be applied to the quick diagnosis of tumors and the identification of biomarkers. The epidermal cell gap of intra-tumor blood vessels is larger than that of normal blood vessels due to the tumor's rapid growth, and because the tumor lacks a lymphatic system, it is simple for nanoparticles to "leak" into the tumor from the gap in the tumor blood vessels and build up there. According to certain studies, nanomaterials can be directed against the tumor blood vessel endothelial cells, releasing anti-angiogenic medications that effectively inhibit tumor blood vessel growth and lower oxygen delivery. [14] Additionally, nanotechnology takes advantage of the unique chemical and physical properties of the tumor microenvironment, including hypoxia, abnormal temperature gradients, weak acidity, overexpressed proteins and enzymes, and a reduced environment. These special characteristics allow for precise regulation of the drug delivery rate of loaded drugs from nanocarriers. Nanoparticles are sufficiently large to hold several small molecules while still being small in relation to cells. Aptamers, peptides, antibodies, DNA or RNA strands, and other ligands can also functionalize the comparatively vast surface area of nanoparticles. These ligands can be used as medicinal agents or to control how nanoparticles behave in vivo. The administration of many drugs, theragnostic action, and multimodal therapy are made possible by these characteristics. Applying nanoparticles to diseased tissues can make use of their physical characteristics of energy absorption and reradiation, much like those of laser ablation. Therefore, the purpose of this review is to investigate several novel strategies for using nanotechnology to fight breast cancer. An outline

of breast cancer classification, conventional breast cancer treatments, the important characteristics of conventional breast cancer medications, and nanomedicine as a possible alternative drug delivery option for breast cancer therapy are all covered. [15]

**1.1 Classification of Breast Cancer:**

A variety of criteria, including as histology, molecular traits, and the expression of particular biomarkers, have been used to classify breast cancer. [16] The best course of treatment can be chosen once the unique features of breast cancer tumors have been identified. [17] From a molecular standpoint, there are several subtypes of breast cancer, including basal-like, HER2-enriched, normal-like, triple-negative, luminal A, and luminal B. Ten to twenty percent of all cases of breast cancer are of the triple-negative subtype. This condition is more common in women under 40, Afro-descendants, and/or individuals with a BCRA1 gene mutation. [18–20]

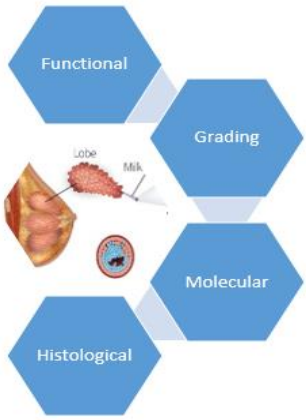


**Figure 1: Types of Breast cancer**

**1.2 Types of Nanoparticles**

As of right now, nanotechnology has advanced quickly to create some of the most significant cancer therapy approaches. Liposomes, micelles, polymeric nanoparticles, solid lipid nanoparticles, and gold nanoparticles are the most often utilized types of nanoparticles in the treatment of breast cancer. [21]

**1.2.1 Liposome:** One of the most popular nanocarriers for medication delivery is liposomes. Liposomes are concentric spheres of phospholipid bilayers that range in size from nano to micro. They are divided by aqueous compartments. In order to protect phospholipids' hydrophobic tails from watery surroundings, liposomes adopt this bilayer structure. [22]

Stable formulation, enhanced pharmacokinetics, and some "passive" or "physiological" targeting to tumor tissue are all advantages of liposomal drug delivery methods. Nevertheless, tumor cells are not the direct target of these carriers. In addition to shielding liposomes from unwanted interactions with cell membranes and plasma proteins, the design changes that set them apart from reactive carriers like cationic liposomes also stop interactions with tumor cells. As a drug-loaded depot, liposomes instead stay in the tumor stroma after extravasating into tumor tissue. Eventually, liposomes are attacked by phagocytes and/or enzymes, which releases the medication for later diffusion to tumor cells. Direct molecular targeting of cancer cells through antibody-mediated or other ligand-mediated interactions is a hallmark of the upcoming generation of drug carriers. [23, 24]

Immunoliposomes are a method of molecularly targeted drug administration in which mAb fragments are attached to liposomes. Either Fab' or scFv fragments connected to long-circulating

liposomes have been used to create anti-HER2 immunoliposomes. Anti-HER2 immunoliposomes effectively adhered to and absorbed in HER2-overexpressing cells in preclinical investigations, enabling effective intracellular delivery of encapsulated drugs. Polymer systems are also being developed in conjunction with antibody-based targeting. Similarly, liposomes and polymers are being used in conjunction with ligand-based targeting that uses growth factors, hormones, vitamins (including folate), peptides, or other particular ligands. [25, 26]

**1.2.2 Micelles:** It is known that polymeric micelles are "well-formed auto-assemblies" that form in a liquid matrix made up of amphiphilic macromolecules. Typically, di- or tri-block copolymers with both solvophilic and solvophobic blocks comprise these amphiphilic macromolecules. [27] Polymeric micelles are typically between 10 to 100 nm in size. The hydrophilic chain of the polymeric micelles covers the hydrophobic center. Self-assembling micellar structures of the plant-based polymer inulin (Inutec-SP1®, INT) were created by Kesharwani et al. [28] The anticancer effects on breast cancer were investigated by loading these nanocarriers with a combination of doxorubicin and paclitaxel (DOX and/or PTX). Superior drug loading efficiency and sustained drug release were exhibited by the INT-formed micelles. [29] Through the clathrin-mediated process of endocytosis, the micelles entered tumor cells and were subsequently carried to lysosomes, where they released medicines. Comparing this system to other systems, the combination of DOX and PTX shown improved antitumor potential. These micelles also demonstrated targeted delivery at the tumor site and a longer in vivo circulation duration. [30] This novel approach shows promise in treating breast cancer more effectively than free drugs. [31]

**1.2.3 Polymeric nanoparticles**

Third-generation polymeric nanocarriers became available with unique properties. These third-generation nanocarriers are functionalized with a special ligand that may attach to the overexpressed receptor and use the active mechanism to deliver drugs. Recently, PNPs have emerged as one of the most viable and promising technology platforms for achieving multifunctional, environment-responsive, targeted, and controlled drug delivery systems. [32] Because of their nanoscale size and capacity for regulated drug release and selective targeting, polymeric nanoparticles (NPs) seem to be the most promising drug carriers. It has been extensively documented that NPs in the 100–400 nm range accumulate at the tumor site via the increased permeability and retention (EPR) effect. [33] This promotes high drug accumulation, which makes it easier for convection and diffusion mechanisms to deliver the medication to the target region while also reducing tissue harm. The NPs' surface charge and size have a significant impact on passive targeting. Both characteristics are crucial for the NP's circulation duration and retention in the tumour. [34] The so-called active targeting can even boost drug efficiency after it has accumulated in the tumor area. NPs can actively target tumour cells by binding to overexpressed receptors on target cells that are either weakly expressed or not expressed at all on normal cells. By avoiding healthy tissues and delivering the medication to the intended site, actively targeted nanoparticles (NPs) improve therapeutic efficacy. [35] For instance, it is anticipated that NPs containing the monoclonal antibody trastuzumab, which interacts with the surface protein HER2, will gather at locations where HER2 is overexpressed, such as in cancers of the breast or stomach. These particles can be loaded with additional substances, such taxanes, which work in concert with trastuzumab to treat breast cancer. [36, 37]

**1.2.4 Solid lipid nanoparticles**

For oral administration, SLNs were presented as a unique drug carrier system. SLNs have garnered particular attention in the treatment of cancer over time. SLNs in particular offer a number of benefits, including as high drug content capacity, exceptional physical stability, an excellent release profile and biocompatibility.[38] Cell proliferation was successfully reduced by MCF-7 cells treated with cisplatin-SLN. When compared to free cisplatin, which had an IC50 value of 10 µg/mL, cisplatin-SLNs demonstrated strong cytotoxic effects in MCF-7 cells (6.51 ± 0.39 µg/mL), but not in normal cells. [39] These findings show that cisplatin-loaded SLNs have successfully circumvented the toxicity and restrictions of conventional delivery techniques in breast cancer patients. [40–43]

### 1.2.5 Gold Nanoparticle:

Applications for gold nanoparticles in breast cancer detection are numerous and include non-invasive in vivo imaging and pathology specimen evaluation. Park et al. discovered that tumor cells embedded with gold may be seen in vivo using two-photon-induced photoluminescence (TPIP). Normal breast cells were not visible after trastuzumab-PEG-AuNS therapy, while HER-2 positive SK-BR-3 cell lines were visible with 10% of the highest laser power in TPIP imaging. [44] Furthermore, Bickford et al. discovered that reflectance confocal microscopy images of tissue treated with AuNS conjugated with PEG and an anti-HER-2 antibody produced results that matched those of hematoxylin-and-eosin staining and classical immunohistochemistry in an investigation of the ex vivo assessment of the surgical resection margins of breast-conserving surgery. It reduced the imaging preparation time to five minutes, increasing the possibility of clinical translation by enabling real-time frozen section examination during surgery. [45,48]

## 2. Nanoparticles used in breast cancer

| Sr No. | Type of nanoparticle used | Drug used | Author | year | Conclusion | References |
|---|---|---|---|---|---|---|
| 1 | Polylactide-co-glycolide (PLGA) based nanoparticles | Tamoxifen citrate | Ruma Maji et al. | 2014 | In vitro, the MCF-7 breast cancer cell line absorbed tamoxifen nanoparticles well, exhibited the maximum drug loading, and released the drug continuously for an extended length of time. | [49] |
| 2 | solid lipid nanoparticles | Quercetin | Firoozeh Niazvand et al. | 2019 | In MCF-7 cells, SLN efficiently enhanced the cytotoxic effects of QT by triggering oxidative stress and activating the intrinsic apoptotic pathway. | [50] |
| 3 | polymer-based nanoparticles | Letrozole | Bayan Alemrayat et al. | 2018 | The formulation's LTZ concentration affects the physiochemical characteristics, among other things. The possibility of producing novel LTZ formulations for monthly administration—possibly as IT or IM injections—was suggested by the in-vitro release study. Future in vivo research is unquestionably required to examine the viability of this idea. | [51] |
| 4 | PLGA Nanoparticle | paclitaxel and thymoquinone | Parth Soni et al. | 2014 | The effective uptake of nanoparticles in MCF-7 cells also implies that the drug will be | [52] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | released by the nanoparticles inside the cells rather than outside, raising the drug's intracellular concentration. | |
| 5 | Liposome | gemcitabine (GEM) and tamoxifen | D. Cosco et al. | 2012 | Liposomes embedded with tamoxifen and gemcitabine (GEM) enhanced the antitumoral impact. | [53] |
| 6 | polymeric micelles | Resveratrol | Yiota Gregoriou et al. | 2021 | The resultant nanoparticle did not significantly absorb into immortalized healthy epithelial cells, but it was successful in specifically targeting aggressive forms of breast cancer. Furthermore, the nanoparticle significantly decreased the viability of breast cancer cells while having no discernible harmful effects on immortalized breast cells. | [54] |
| 7. | Self-assembled polymeric micelles | Teniposide | Bingyang Chu et al. | 2016 | Additionally, teniposide micelles improved the dispersion in tumors in vivo and the cellular absorption by MCF-7 breast cancer cells in vitro. | [55] |

**3. Marketed Formulation**

| Sr. No | Product | Company Name | Therapeutic agent | Nanotechnology | Route of administration |
|---|---|---|---|---|---|
| 1 | Abraxane | American Bioscience Inc. | paclitaxel | Nanocrystal formulation | IV |
| 2 | Myocet | CHEPLAPHARM | Doxorubicin | Liposome | IV |
| 3 | Caelyx | Johnson & Johnson | *doxorubicin hydrochloride* | pegylated liposomal formulation | IV |
| 4 | Genexol-PM | Lupin Ltd | Paclitaxel | Polymeric micelle | IV |

**4. Future Perspective:**

The most prevalent malignancy among women is breast cancer. Since breast cancer is a diverse disease, various treatment plans are now employed based on patient compliance, stage, and breast cancer subtype. However, not all patients respond well to the existing treatments; Triple negative breast cancer (TNBC) is the less responsive subtype. As a result, patients may eventually have recurrences with severe health issues. The scientific community has recently worked hard to discover more effective methods. However, few nanotherapeutics make it to clinical usage despite the promising promise of nanoparticles in breast cancer therapy because of complicated designs, manufacturing difficulties, regulatory barriers, prices, and testing limitations. To get beyond these obstacles, new regulations must be put in place as nanotherapeutics play a bigger role in diagnosis and treatment. [53] Although targeted cancer therapy with nanoparticles has a lot of potential, there are a few obstacles that need to be overcome. These include the possible toxicity of nanoparticles, the challenge of managing drug release, and the possibility of nanoparticle clearance by the immune system. Nonetheless, it is projected that

nanoparticle-based cancer treatments will play a significant role in oncology in the future with continued study and development. To sum up, tailored nanoparticles present a novel and promising strategy for targeted breast cancer treatment that could significantly improve patient outcomes. However, more research and clinical trials are necessary to fully understand their potential and constraints. [55]

## 5.CONCLUSION:

Research on using nanoparticles to treat breast cancer has grown significantly in recent years, with a primary focus on employing targeting ligands to obtain high accumulation with tumors. HER2 is one of the most prevalent cell surface receptors on breast cancer cells, and conventional anticancer medications like doxorubicin, docetaxel, and paclitaxel work well against this receptor. Compared to nanoparticles without targeting ligands, treatment efficiency is raised and toxicity in healthy cells is prevented when targeting ligands are used in the nanoparticle production process. Enhancing drug transport, release, and targeting with nanotechnology has great promise for increasing therapeutic efficacy and reducing side effects. Targeting medications based on nanomaterials may benefit patients with breast cancer and mark a significant advancement in the disease's detection and therapy.

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