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A QUICK OVERVIEW OF NANOMEDICINE APPLICATIONS IN BREAST CANCER DETECTION, IMAGING, AND THERAPY

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Review Article

Breast cancer continues to be a global public health dilemma and is currently the most prevalent tumor in the world. Breast cancer awareness, public attention, and progress in the breast imaging have had a positive impact on breast cancer recognition and screening. Breast cancer is a fatal disease in females and the leading cause of death in females. Over the past two decades, studies related to breast cancer have guided amazing advances in our understanding of breast cancer, leading to more competent treatments. Among all the malignant diseases, breast cancer is one of the most common causes of mortality among postmenopausal women, accounting for 23% of all cancer fatalities. This is a global problem today, but it is still diagnosed in its advanced stages due to women's neglect concerning about the self-inspection and clinical examination of the breast. This review presents different types of breast cancer, symptoms, risk factors, epidemiology of breast cancer, stages of breast cancer, diagnostic investigations, and treatment. Chemotherapy, targeted therapies, surgery, radiation therapy, hormone replacement therapy, complementary therapies, gene therapy, and stem-cell therapy are some of the treatments for breast cancer. In this review, various applications of nano-carriers were discussed such as nanopolymers, Nanoshells, nanocrystals, quantum dots, and dendrimers were examined, as well as their potential in early cancer diagnosis and therapy.

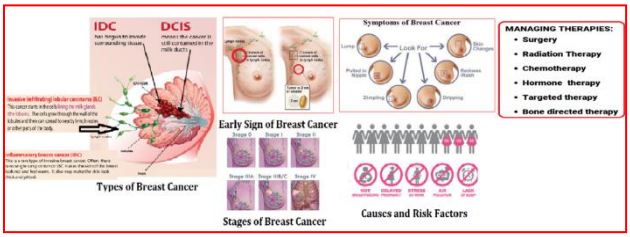

Fig. 1. Graphical Abstract

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Keywords: Nanomedicine; Cancer detection; Cancer Treatment; Chemotherapy; Tumors; Nanoshells.

1. INTRODUCTION

Breast cancer is a common cause of cancer in women, making it the second most common explanation for cancer death in women in the United States. Normally, cancer is named after the part of the body in which it originated; breast cancer refers to cancer from breast tissue most commonly from the internal mucosa of the milk ducts or lobules that provide milk to the ducts. Awareness of breast cancer is very important for early detection, often through screening, can catch the disease when it is most treatable [1]. Worldwide, breast cancer comprises 10.4% of all cancer incidences among women, and 5th commonest explanation for cancer death [2]. In 2004, breast cancer caused 519,000 deaths. Breast cancer is more common in the left breast than in the right [3]. Most breast cancers are found in women who are 50 years old and older [4]. The highest incidence of breast cancer was in Belgium with 113.2 per 100,000 and the lowest incidence was in Asia and Africa [5].

Cancer cells are very almost like cells of the organism from which they originated and have similar DNA and RNA that is often detected by the immune system. The mutations of DNA/RNA occur due to electromagnetic radiation, X-rays, gamma rays, free radicals, aging of DNA, RNA, etc [6]. Cancer is also called entropic disease where the organism cannot correct this itself; external intervention is required to permit the organism to return to a stable entropic stage. Invasive ductal carcinoma and invasive lobular carcinoma are the two most frequent kinds of breast cancer, about 70-80 percent of all breast cancers are invasive ductal carcinomas [7].

1.1 Breast Cancer Types

Various types of breast cancer like Noninvasive, Ductal carcinoma in situ and Invasive breast cancer according to sites represented in Fig. 2.

Noninvasive: Cells that are restricted to ducts and do not infiltrate the breast's adipose and connective tissues [8].

The most frequent kind of carcinoma is ductal carcinoma in situ (DCIS), whereas lobular carcinoma in situ (LCIS) is less prevalent but increases the risk of breast cancer [9].

Invasive breast cancer: Breast cancer that has broken through the duct and lobular walls and entered the fatty and connective tissues of the breast is known as invasive breast cancer. Cancer does not have to spread to the lymph nodes to be invasive [10].

1.2 Commonly Occurring Breast Cancer [11]

- LCIS (Lobular carcinoma in situ)
- DCIS (Ductal carcinoma in situ)
- ILC (Infiltrating lobular carcinoma)
- IDC (Infiltrating ductal carcinoma)

1.3 Infrequently Occurring Breast Cancer [12-13]

- Inflammatory breast cancer
- Paget's disease of the nipple
- Phyllodes tumor
- Medullary carcinoma
- Mutinous carcinoma
- Tubular carcinoma

1.4 Early Sign and Symptoms of Breast Cancer

A lump in the breast is a typical sign of breast cancer. Breast self-examination (BSE) on a monthly basis is a good way to get to know the texture, cyclical changes, size, and skin condition of the breast. Swelling in the breast, armpit (lymph nodes), nipple discharge, pain in the nipple, nipple, scaly or pitted skin on the nipple, persistent tenderness of the breast, and unusual breast pain or discomfort are general altering features of breast cancer, early sign and symptoms of breast cancer are represented in Fig. 3. Underarm lymph nodes are present in advanced stages of disease along with other symptoms such as bone metastases, shortness of breath, and lack of appetite, inadvertent weight loss, headaches, neurological pain and weakness [14].

The stage aids doctors in determining the best therapy and prognosis. Breast cancer stages are classified as in situ (non-invasive) or invasive (invasive) [15]. Stages can be defined in great depth and assigned a numerical designation (0 to 4) different stages and 5 years survival rate represented in Fig. 4.

Stage 0: Breast cancer that isn't invasive and hasn't spread to the tissues

1: It's less than 2cm in diameter and hasn't migrated to the lymph nodes.
2: 2A - ≤2cm and has spread to lymph nodes
2 B – 2 to 5cm and has spread to lymph nodes and ≥ 5cm has not spread to lymph nodes.

3: 3A – ≤5cm and spread to lymph nodes forming clumps (or) ≥5cm and spread to lymph nodes without forming clumps.
3 B- Any size, spread to the skin or chest wall.
3 C- Any size and spread to lymph nodes, skin and the chest wall
4: The disease spreads to other organs or tissues, such as the lungs or lymph nodes.

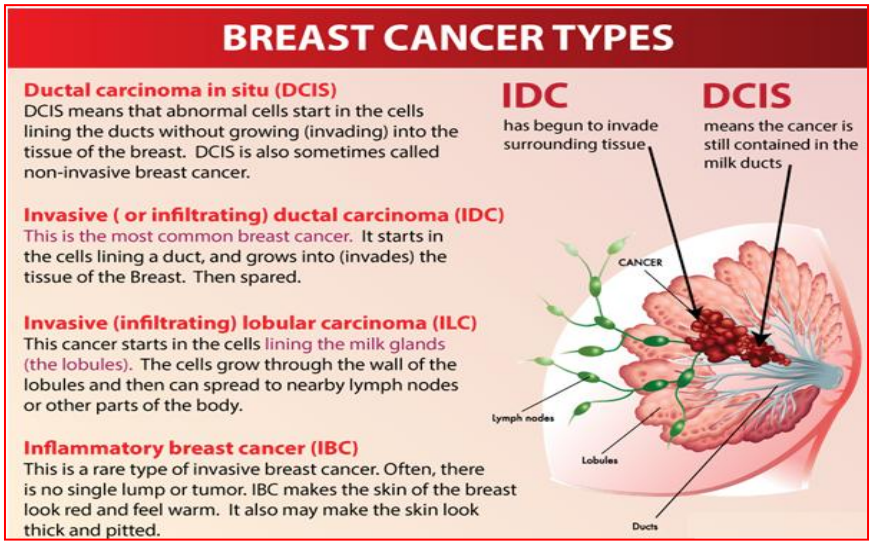

Fig. 2. Types of Breast Cancer (imported from https://drjockers.com/breast-cancer/)

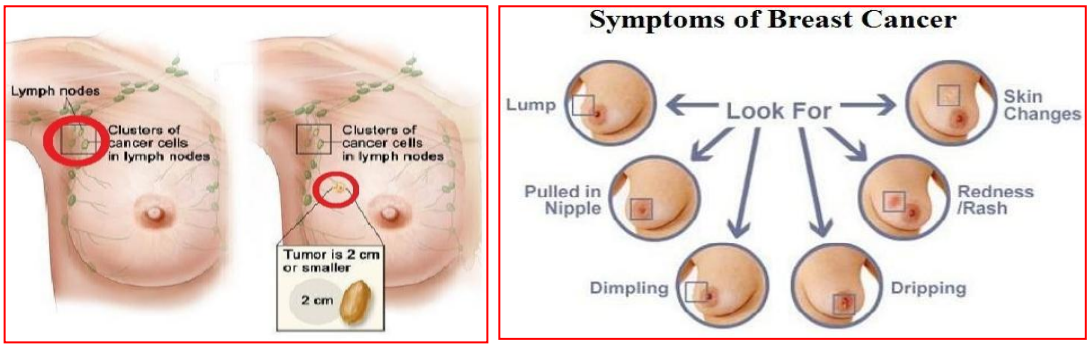

Fig. 3. Early Sign and Symptoms of Breast Cancer (Imported from https://www.genuinedrugs123.com/Blog-142-Evolving-role-of-zoledronic-acid-in-early-breast-cancer.aspx, https://medluxinternational.com/breast-cancer/signs-and-symptoms-of-breast-cancer/)

Stages

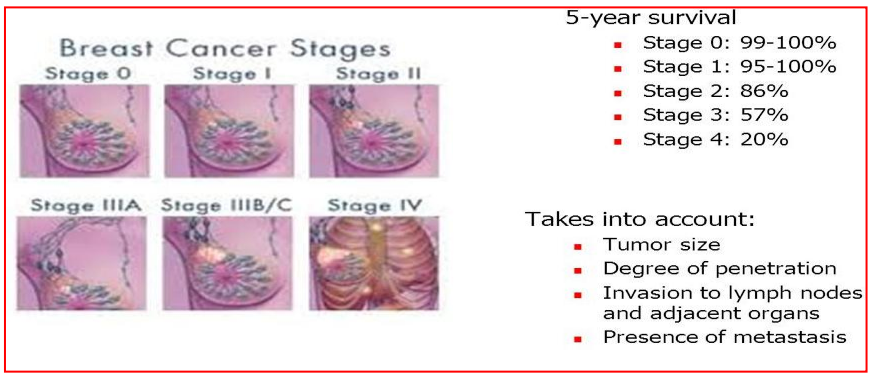

Fig. 4. Different Breast Cancer stages and 5 year survival rate (Imported from https://pt.slideshare.net/prarthnabhardwaj7/breast-cancer-awareness-40802925)

2. CAUSES AND RISK FACTORS [16-24]

Age: In India the average age for cancer patients is around 20-30 years, which is 10 years less when compared to developed countries [16].

Family History: If there is a family history of breast cancer, subsequent generations are at risk for the illness. Approximately 5-10% of all breast cancer occurrences are inherited, particularly in parents who have a defective gene [17, 18].

Late Menopause: After the age of 45, menopause raises the risk of cancer [19].

Early Menstruation: Your age when you first started menstruating may be connected to your lifetime risk of breast cancer [20].

Delayed or No Pregnancy: A woman who gives birth has a 30 percent less chance of getting breast cancer as compared to a woman who has never conceived [20].

Obesity: Being overweight or obese can increase the risk of breast cancer in women who have gone through menopause [21].

Breastfeeding: Breastfeeding decreases the risk of breast cancer by 4%.

Birth Control Pills: Using birth control pills for a long time can expose women to the risk of breast cancer [22].

Breast Tissue Composition: Breast density, to some extent, contributes to the overall risk of developing breast cancer [23].

Hormone replacement therapy: Hormone therapy is required by certain women to relieve a few symptoms of menopause. Women who take combined hormone therapy increase their risk for breast cancer" [24]. Various causes and risk factors of Breast cancer on career women are represented in Fig. 5.

2.1 Diagnosis

Mammograms: It is an X-ray of breast cancer that uses a very small amount of radiation.

Breast Ultrasound: It uses sound waves to outline a part of the body. The wave echoes are picked up by a computer to create a picture on the computer screen.

Breast MRI Scan: It uses magnets and radio waves. It takes cross-sectional images of the body and takes a long time.

Biopsy: It is done when other tests show that you might have breast cancer and confirms of a mass is cancerous, mass is removed and studied.

Clinical Breast Exam: Women who are in their 20s and 30s should have this exam for every 3years and after 40years they should have a breast exam every year.

Breast Self-Exam: It is an exam which is manual inspection and any changes detected should be reported to a medical expert [25, 26].

Managing Therapies: Various managing therapies like surgery, radiation, chemotherapy, hormone, targeted, and bone-directed therapy are using for breast cancer. Various types of breast cancer treatment are represented in Fig. 6.

Fig. 5. Causes and Risk Factors of Breast cancer on Career Women (Imported from https://visual.ly/community/Infographics/health/top-5-causes-breast-cancer-career-women)

2.2 Surgery

Depending on the stage and sort of the tumour, ablation (or) surgical removal of the whole breast is performed. If the removed tissue doesn't have clear margins, more operations to get rid of additional tissue could also be necessary this might generally need the removal of a part of the greater pectoral muscle which is the main muscle of the anterior chest wall. Recently, the technique of watchman lymphatic tissue dissection has become well-liked, because it needs the removal of so much fewer humour nodes, leading to fewer facet effects. Advances in watchman lymphatic tissue mapping over the past decade have enhanced the accuracy of detection of watchman lymphatic tissues [27,28]. Various types of surgery applied for breast cancer are represented in Fig. 7.

Lumpectomy: Breast-conserving surgery (or) partial segmented mastectomy. It is the surgical removal of tumour and a small margin of healthy tissue around it and followed by radiation therapy.

Mastectomy: Surgically removing the breast and other injected components. A case study was represented in Table 1.

Quadrantectomy: Removal of one-fourth of the breast.

Radiation therapy: It is a cancer-killing therapy that uses high-energy x-rays (or) particles. The patient may require 3 to 5 treatment each week for 3 to 6 weeks. The sort of radiation therapy utilised is mostly determined by the type of breast cancer [29,30]. Case study was represented in Table 1.

Breast radiation therapy: It is applied after a lumpectomy [31]

Chest wall radiation therapy: It is applied after a mastectomy [31]

Breast boost: The area where the tumour was surgically excised receives a high dosage of radiation treatment [32].

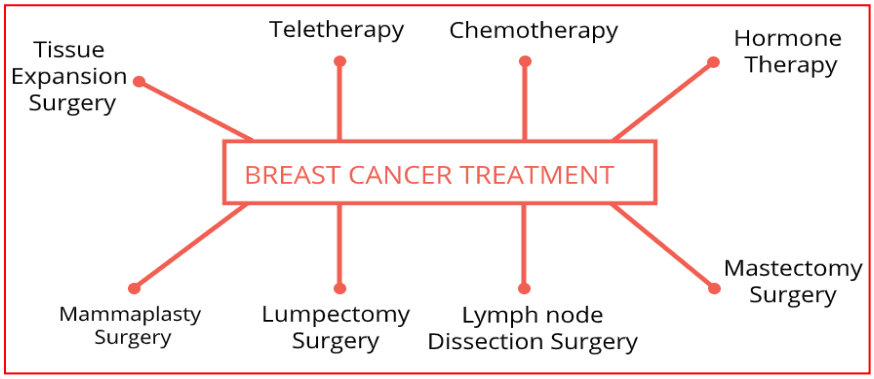

Fig. 6. Various types of Breast Cancer treatment

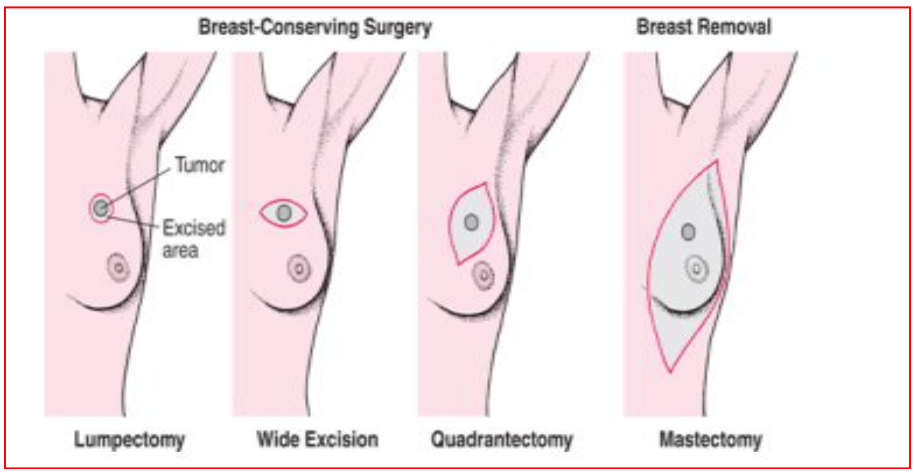

Fig. 7. Various types of surgery applied for Breast Cancer

Lymph nodes radiation therapy: It is used to eliminate cancer cells that have spread to the axillary lymph nodes and the surrounding region [32].

Brachytherapy: Radiation to the breast by implanting radioactive seeds into the breast tissue [33].

Chemotherapy: It is the administration of cancer-killing medications intravenously as a shot or orally as a tablet or liquid. A case study was represented in table 1 [31-33].

Hormone blocking therapy: HBT is a therapy used by doctors to keep hormone-sensitive breast tumours from recurring following treatment. Estrogens receptor-positive and progesterone receptor-positive malignancies may be treated with hormone treatment. Examples like tamoxifen aromatise inhibitors, ovarian ablation or suppression, goserelin which is luteinising hormone releasing agonist drug that suppress the ovaries [34].

Targeted therapy: It employs specific drugs that are known to target the certain proteins or enzymes involved in cancer cell proliferation. The most well-known of the targeted medicines Herceptin (trastuzumab), is used to treat HER2-positive breast cancer. Perjeta (pertuzumab), Kadcyla (T-DM1), and Tykerb (lapatinib) are some of the other targeted medicines available to treat HER2-positive metastatic breast cancer [34,35].

Breast cancer molecular subgroups and current conventional medication treatment: Trastuzumab (Herceptin), a humanised anti-HER2 monoclonal antibody, is the most well-known targeted treatment to date. At the moment, adjuvant medication treatment is primarily determined by the intrinsic subtype of breast cancer [36]. Table 2 summarizes the current standard drug therapy options.

Applications of Nanomedicine in Breast Cancer Detection, Imaging, and Therapy: Nanotechnology has the potential to improve breast cancer treatment by improving the delivery of medicine to tumour locations. Several mechanisms can be used to carry out this delivery: Active targeting via conjugating tumour specific targeting ligands to nanoparticles, and direct tumour administration by injection, photodynamic treatment, and radiation. Passive targeting that makes use of local features of the tumour environment [37,38]. The summary of various nanotechnology treatment approaches for breast cancer is highlighted in Tables 3, 4, and 5.

Table 1. Case studies of Breast Cancer

S. No	Patient Age	Problem	Therapy Used	Observation	Reference
1	58	2 CM mass in one of her breast	Radiotherapy	There is no signs of abnormal cell growth	29
2	42	Bloody nipple discharge	Ductal excision	No bloody discharge after therapy	30
3	35	Ductal carcinoma	Mastectomy	Reconstitution of breast tissue	31
4	65	Red swollen breast and orange skin and enlarged lymph nodes	Chemotherapy	Enlarged lymph nosed is reduced.	32, 33

Table 2. Current conventional drug therapy

Molecular subtype	Other conditions	Hormone Therapy	Chemotherapy	Anti-HER2
Luminal A	Low tumor burden	+	-	-
	High tumor burden* or grade 3	+	+	-
Luminal B	HER2+	+	+	+
	HER2−	+	+	-
HER2 Positive	NA	-	+	+
Triple Negative	NA	-	+	-

*Note: HER2-Human Epidermal Receptor 2; *≥4 positive LN, LN- Lymph Nodes; NA-Not Applicable; +-Yes; - No*

Table 3. Nanotechnology treatment modalities for breast cancer

Nanoparticles	Modality	Short description	Reference
Liposomal Particles	Passive targeted therapy	Doxorubicin coupled onto liposomal nanoparticles	[39]
PLGA poly(lactic-co glycolic acid)	Actively targeted therapy	Coupled with efflux pump inhibitor and chemotherapeutic agent	[40]
Liposome's	Drug delivery	Organic nanoparticles Lipid layered colloid structure	[41]
Quantum dots	Detection; imaging (multichromatic)	A cadmium-selenide core is surrounded by a zinc-sulfide shell, has fluorescent and photodynamic properties; alternative to FISH; sentinel lymph node identification; 2–10 nm	[42-44]
Carbon nanotubes	Sentinel node visualization; drug delivery	Contains carbon	[41]
Dendrimers	MRI contrast agent; gene delivery; drug delivery	Branched macromolecule	[41]
Chitosan particle	Passive targeted therapy	Chitosan bonded to 5-fluorouracil increased cytotoxic effect of chemotherapy on tumor cells	[45]
Sirolimus conjugated to PLGA	Actively targeted therapy	Decreases sirolimus toxicity allowing its use	[46]

Table 4. Various Applications of Nanocarrier for treatment of breast cancer

Nanocarrier	Therapeutic Agent (s)	Key Indication	Reference
Gold–gold sulfide nanoparticles linked to the HER2 antibody	Gold–gold sulfide for high intensity photoablation	Nanoparticles can attach to SK-BR-3 cells that are over expressing HER2, causing cancer cells to become thermally damaged in seconds.	[47]
Mini nanodrug based on polymalic acid	Antisense oligonucleotides	The polymer-attached trastuzumab-mimetic 12-mer peptide recognises HER2+ cells. HER2/neu receptors were down regulated, resulting in a 15-fold reduction in tumour growth compared to the control group.	[48]
Combinational system of HER2 immunoliposomes/liposomes	Bevacizumab in liposome; doxorubicin in immunoliposome	In HER2/MDR double-positive breast cancer, the combination had the best growth suppression and the least toxicity. Tumor size decreased slowly within 60 days	[49]
A pH-responsive nanocarriers			
Liposome's that respond to pH	Paclitaxel	In an acidic pH, paclitaxel releases faster and is more effective in vitro and in vivo on breast cancer models.	[50]
Glycolipid-like nanocarrier made from chitosan	Doxorubicin	MCF-7 breast cancer cells are more cytotoxic than SKOV3 ovarian cancer cells because the former has a more acidic extracellular environment.	[51]
Block copolymer nanoparticles with acidity-sensitive linking bridges	Small interfering RNA	Due to the hydrophobic PLGA layer, the PEG surface layer separated in response to tumour acidity to aid cellular absorption, and siRNA was promptly released into tumour cells.	[52]
Targeting of tumor-associated macrophages			
Mannose-coated PLGA nanoparticles	Doxorubicin	The anticancer impact of nanoparticles is significantly improved in triple-negative breast cancer, indicating TAM depletion.	[53]
Liposomal nanoparticles that target legumains	Hydrazinocurcumin	TAM was "re-educated" and shifted to M1-like macrophages when STAT3 activity was inhibited, resulting in reduction of 4T1 cell motility and invasion in vitro and suppression of tumour development, angiogenesis, and metastasis in vivo.	[54]
Abraxane	Paclitaxel	Abraxane may enhance the CD80+ CD86+ M1 macrophage subpopulation and operate against M2 cells in addition to targeting EPR and gp60 to deliver additional anticancer effects.	[55]

Table 5. Various types of Breast Cancer treatment by using Nanocarrier [56]

Type	Target	Nanocarrier	Therapeutic Agent (s)	Key Indication	Reference
Triple-negative	Folate receptor	Micelles of copolymer micelles that have been functionalized with folate	Orlistat	PARP inhibition has been shown to have anticancer properties in vitro and in vivo.	[57]
		Folate-conjugated liposomes	Benzoporphyrin derivative	The MDA-MB-231 cell model, both monolayer and three-dimensional, was more responsive to the targeted formulation.	[58]
	EGFR	Immunoliposomes decorated with anti-EGFR antibody	Doxorubicin	Phase I study indicated good tolerability and recorded clinical activity	[59]
		RNA-NPs with an aptamer that targets EGFR	Anti-miRNA	In an orthotopic TNBC tumour model, there was a significant buildup of NPs with impaired renal and hepatic clearance.	[60]
Stem cell therapy	CD133	Anti-CD133 antibody coated PLGA nanoparticles	Paclitaxel	Effective in reducing the amount of paclitaxel-resistant MDA-MB-231 mammospheres and colonies.	[61]
	CD44	Hyaluronic acid-coated PLGA nanoparticles	Salinomycin and paclitaxel	Hyaluronic acid surface coating resulted in a 1.5-fold increase in absorption into CD44 MDA-MB-231 cells and the greatest in vitro activity.	[62]
		Chitosan-decorated Pluronic F127 nanoparticles	Doxorubicin	The delivery of doxorubicin to CD44 cells was significantly improved, with significant cytotoxicity.	[63]
Tumor microenvironment	MMP-9	Liposome with degradable lipopeptides	Carboxyfluorescein as fluorescent dye	MMP-9 degrades lipopeptide, resulting in a significant increase in release rate in the presence of MMP-9.	[64]
	MMP-2	Liposome modified with chlorotoxin	Doxorubicin	Chlorotoxin modified liposomes had increased in vitro toxicity and in vivo targeting efficiency to 4TI tumours, and might inhibit lung metastasis with minimal systemic toxicity.	[65]
	Stromal cells	Cellax® (nanoparticles of acetylated carboxymethylcellulose linked with PEG)	Docetaxel	In many studies, it was found to have a greater MTD and reduced tumour growth and metastasis than Abraxane.	[66]
				xenograft models; additionally, lowered -smooth muscle actin content by 82 percent and 70 percent in the 4T1 and MDA-MB-231 models, respectively.	[67]

3. CONCLUSION AND FUTURE PROSPECT

In Indian women, the most common type of cancer is breast cancer. Breast cancer accounts for 25 to 31% of all cancers in women in India. As a result, all women should undertake monthly breast self-exams, as the early indications of breast cancer are often undetectable. This self-exams can help you detect any changes in your breasts and give you plenty of time to visit your doctor. Remember, discovering an abnormality too late can be fatal. The fact that there are millions of cancer survivors all across the world proves a crucial point. It indicates how cancer, even in its most severe form, may be defeated by assuring excellent treatment outcomes. In reality, over 90% of newly diagnosed breast cancer patients will live for at least five years. The development of even more effective screening and treatment methods is still under way. Although, owing to the increasing intricacy of the nano formulation, these advanced techniques should be approached with caution. Because the majority of breast cancer nanotherapeutic methods are based on active targeting, although active targeting is theoretically better than passive targeting, combining targeting moieties with nanocarriers increases formulation complexity, this can lead to greater toxicity and immunogenicity, as well as increased manufacturing costs and GMP problems. The same is true for nanoformulations containing several drugs. Scientists developing novel nanoformulations must provide sufficient evidence that the nanoformulation is therapeutically more active, stable, and cost-effective.

Finally, it should be emphasised that when breast cancer spreads, it is the most dangerous and difficult to cure. Breast cancer frequently spreads to the bone, lung, liver, and brain, yet the majority of anticancer treatments, including nano formulations, are inaccessible to these areas. It's important to design nano formulations that can sufficiently permeate all of these locations without producing too many side effects. In the future development of breast cancer nanomedicine, Close collaboration with experts in pharmacokinetics, toxicology, immunology, and oncology is expected to be crucial.

DISCLAIMER

The products used for this review are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the review was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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