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POTENTIAL OF NANOPARTICLES IN THE EFFECTIVE MANAGEMENT OF BREAST CANCER

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Keywords:

Breast cancer, Nanoparticles, Anticancer drugs, Targeted therapy, Drug delivery system

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ABSTRACT: Breast cancer (BC) is one of the most prevalent cancers in women; there were 2.3 million women diagnosed with breast cancer globally. Unfortunately, most anticancer drugs have reported high Potential toxicity, mutagenic and carcinogenic side effects. Existing treatments can neither stop its propagation and/or recurrence nor are specific for cancer cells. Hence the side effects on healthy tissues and cells are common. There is a need to improvise the patient's quality of life and the efficiency of the treatments, which can be potentiated with reduced toxicity. Nanotechnology has vast applications in diagnosing, treating and preventing breast cancer. Nanotechnology offers new alternatives for the design that can be used in cancer treatment and has now become a very promising tool for its use against breast cancer. In this review, we provide a broad overview on the use of nanotechnology in the fight against breast cancer. We have analyzed the latest research (2019-2021) in nanotechnology as a potential step for breast cancer treatment. We also give a brief summary of the research that has been done and some novel developments to show promise for the future growth of nanotechnology in the pharmaceutical field.

INTRODUCTION: Cancer is a group of more than 100 distinct diseases characterized by the uncontrolled growth of abnormal calls in the body. Tumors or neoplasms (from Greek neo, "new," and plasma, "formation"), are abnormal growths of cells arising from malfunctions in the regulatory mechanisms that oversee the cells' growth and development [1]. Cancer forms in the tissues of the breast.

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The most common type of breast cancer is ductal carcinoma, which begins in the lining of the milk ducts (thin tubes that carry milk from the breast's lobules to the nipple). Another type of breast cancer is lobular carcinoma, which begins in the breast's lobules (milk glands). Invasive breast cancer is cancer capable of invading or spreading to surrounding normal tissues of the breast.

Breast cancer occurs in both men and women, although male breast cancer is rare. Extracellular matrix changes that occur in breast cancer tissue are as depicted in **Fig. 1.** The relative importance of cardiovascular disease (CVD) and cancer as leading causes of premature death are examined in the communication.

CVD and cancer are now the leading causes in 127 countries, with CVD leading in 70 countries (including Brazil and India) and cancer leading in 57 countries (including China) [2]. According to reports from the World Health Organization (WHO) in 2019, cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries and ranks third or fourth in a further 23 countries as shown in **Fig. 2** [3].

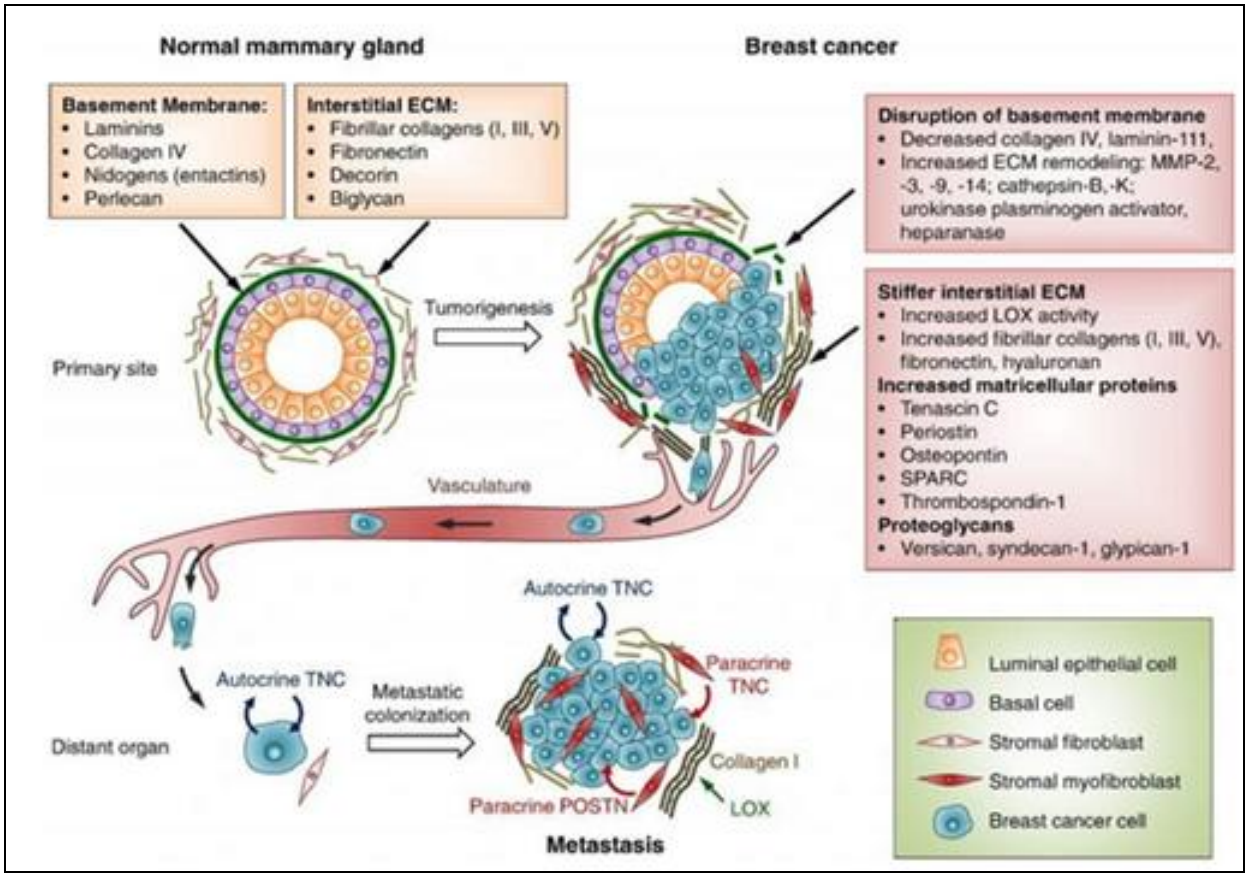

FIG. 1: EXTRACELLULAR MATRIX (ECM) CHANGES IN BREAST CANCER PROGRESSION AND METASTASIS

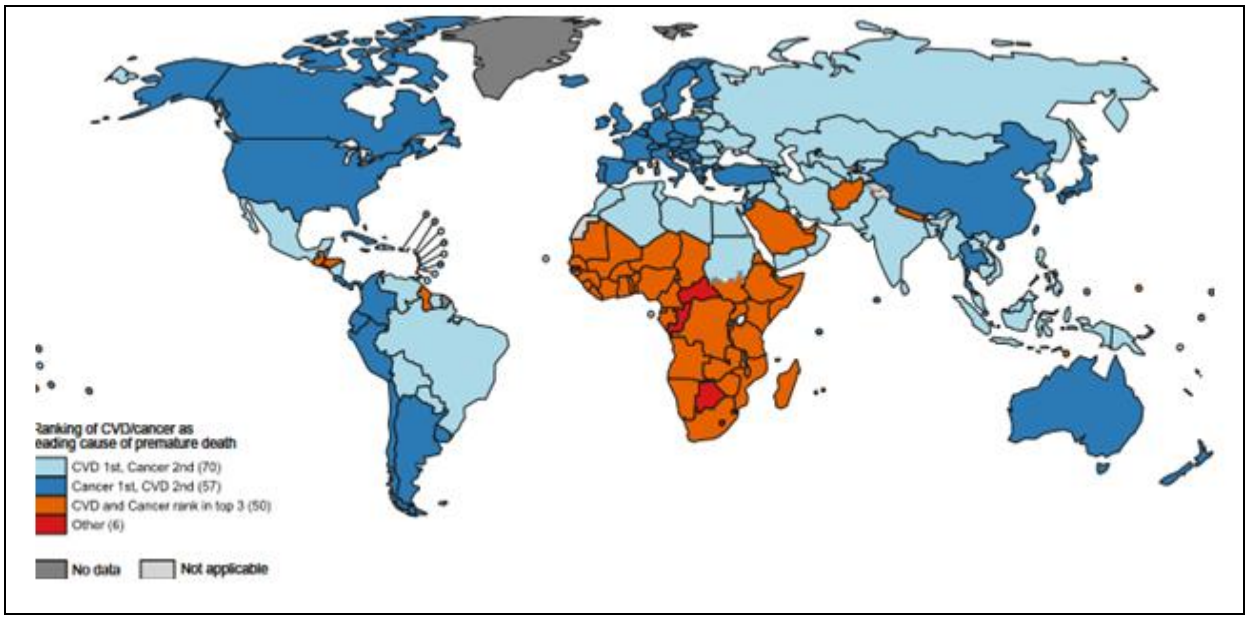

FIG. 2: GLOBAL MAP OF THE RANKING OF CVD AND CANCER AS LEADING CAUSES OF PREMATURE DEATH (AT THE AGES OF 30-70 YEARS) IN 183 COUNTRIES IN 2019. CVD INDICATES CARDIOVASCULAR DISEASE

Breast cancer is the most common cancer in women globally, except for skin cancers. It is about 30% (or 1 in 3) of all new female cancers yearly. The World Health Organization estimates for breast cancer for 2021 is:

- ✓ About 281,550 new cases of invasive breast cancer will be diagnosed in women.
- ✓ About 49,290 new cases of ductal carcinoma in situ (DCIS) will be diagnosed.
- ✓ About 43,600 women will die from breast cancer [4].

Surgery is the mainstay of treatment of the early stages of breast cancer, ranging from lumpectomy to modified radical mastectomy. Surgery typically includes sentinel lymph nodes (LN) dissection for staging the extent of spread into the axilla. Breast cancer recurrences represent a major source of cancer-related deaths [5]. Breast cancer surgery and the associated sentinel LN biopsy result in transient physical discomforts such as pain and numbness in the chest wall, axilla, breast and arm edema. Breast-conserving surgery and breast reconstruction surgeries can address cosmetic concerns after total mastectomy. However, this is often associated with poor body image and other psychosexual problems [6, 7]. Nanotechnology encompasses a broad range of technologies, materials, and manufacturing processes used to design and/or enhance many products, including medicinal products. This technology has achieved considerable progress in oncology in recent years [8]. Nanotechnology yields incredibly small particles of size ranging between tens to hundred nanometers.

These small particles are known as nanoparticles, which are considered engineered materials mainly cluster molecules, atoms, and molecular fragments. These innovations are referred to as nanomedicines by the National Institute of Health and can potentially carry chemotherapeutic agents to the targeted site [9]. Pharmaceutical nanoparticles are solid, submicron-sized (less than 100 nm in diameter) drug carriers that may or may not be biodegradable. The term nanoparticle is a combined name for both Nanospheres and Nanocapsules [10].

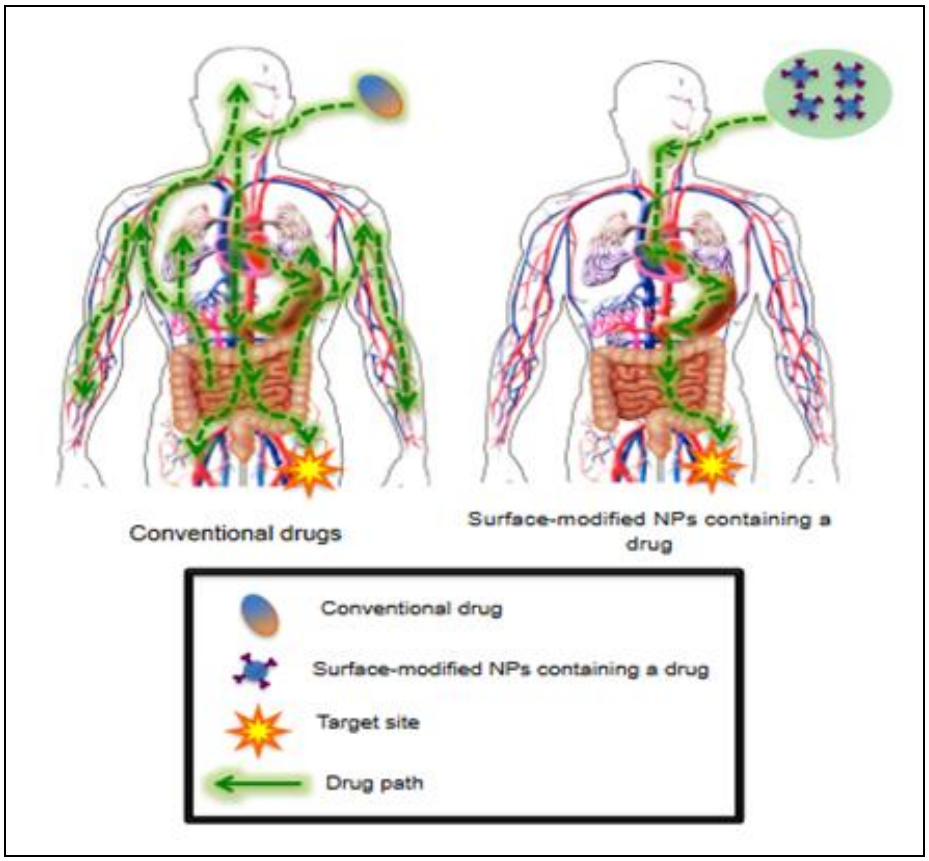

FIG. 3: BODY DISTRIBUTION OF CONVENTIONAL DRUG VS. SURFACE MODIFIED NP'S CONTAINING A DRUG AFTER ORAL ADMINISTRATION

Nanoparticles are submicron (100–1000 nm) sized particles that are generally synthesized from materials such as polymers, lipids, viruses and inorganic materials [11, 12, 13, 14, 15, 16, 17, 18]. NPs are not simple molecules itself and therefore composed of three layers *i.e.* (a) the surface layer, which may be functionalized with a variety of small molecules, metal ions, surfactants and polymers. (b) The shell layer is chemically different from the core in all aspects, and (c) The core, which is essentially the central portion of the NP and usually refers to the NP itself [19]. NPs size can be reduced enough to allow taking advantage of the enhanced permeation and retention mechanism present in tumors, characterized by their characteristic leaky vasculatures [20]. After administration, it is desired that NPs, contrarily to other alternative therapies, have the ability to target a specific anatomical site **Fig. 3**, in order to reduce side effects over healthy tissues [21].

Most of the current anticancer agents do not adequately differentiate between cancerous and normal cells and can lead to systemic toxicity and severe side effects. To overcome limitations of conventional chemotherapeutics, nanotechnology offers a more targeted approach and could therefore provide significant benefits to cancer patients. The size, shape, and charge are important parameters in nanoparticle systems that indicate the *in-vivo* distribution, targeting ability and biological destination of nanoparticles [22]. Nanoparticles have many advantages over free drugs. Some of them are listed below:

- Protect the drugs from early degradation.
- Enhance absorption of the drugs into a selected tissue.
- Control the drug tissue distribution.
- Improve intracellular penetration.
- Prevent drugs from premature interaction with the biological environment.
- Reduce systemic toxicity.

Some important characteristics need to be considered to construct an appropriate Nano carrier for rapid and effective clinical translation. The nanocarriers must be made from a biocompatible material and easily functionalized, well characterized, soluble, exhibit extended circulation ability, no aggregation, and high uptake efficiency by the target cells. Nanocarriers can be classified into three categories based upon the materials that they are made from: (1) lipid-based, (2) polymeric, and (3) inorganic as shown in the below figure. These nanocarriers have been used for a variety of applications such as drug delivery, imaging, apoptosis detection, radiation sensitizers, and photo thermic ablation of tumors [23, 24, 25]. The various types of nanoparticles and their structural organization is as shown in **Fig. 4.**

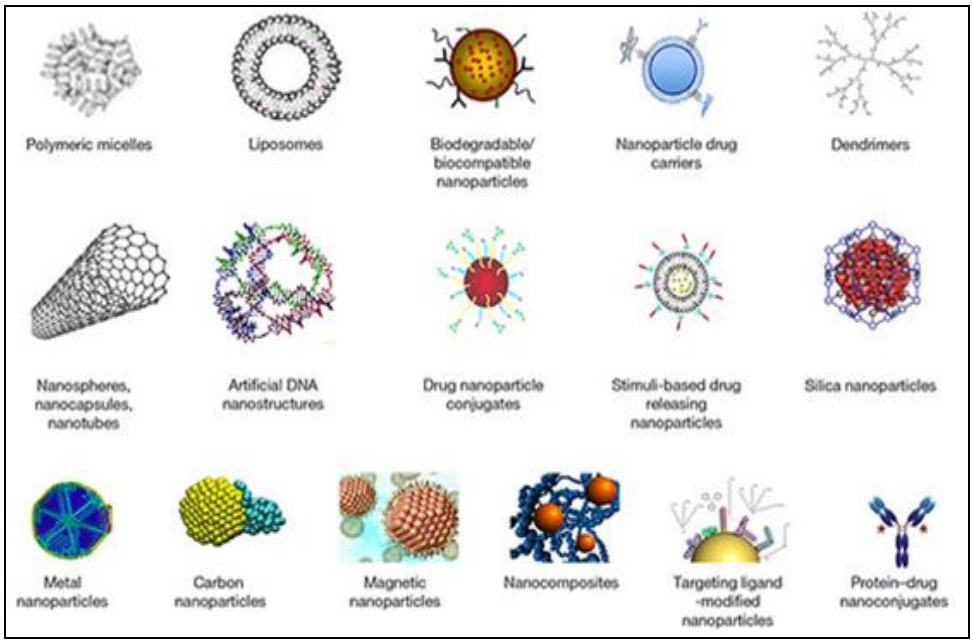

FIG. 4: DEPICTING VARIOUS TYPES OF NANOPARTICLES WITH THE STRUCTURE

Over the last few decades, nanotechnology has been increasingly used in medicine, including applications for diagnosis, treatment, and tumor targeting more safely and effectively. NP-based drug-delivery systems have shown many advantages in cancer treatment, such as precise targeting of tumor cells, reduction of side effects, and drug resistance [26]. The pictorial representation of the nanoparticles-based targeted drug delivery is given in **Fig. 5.**

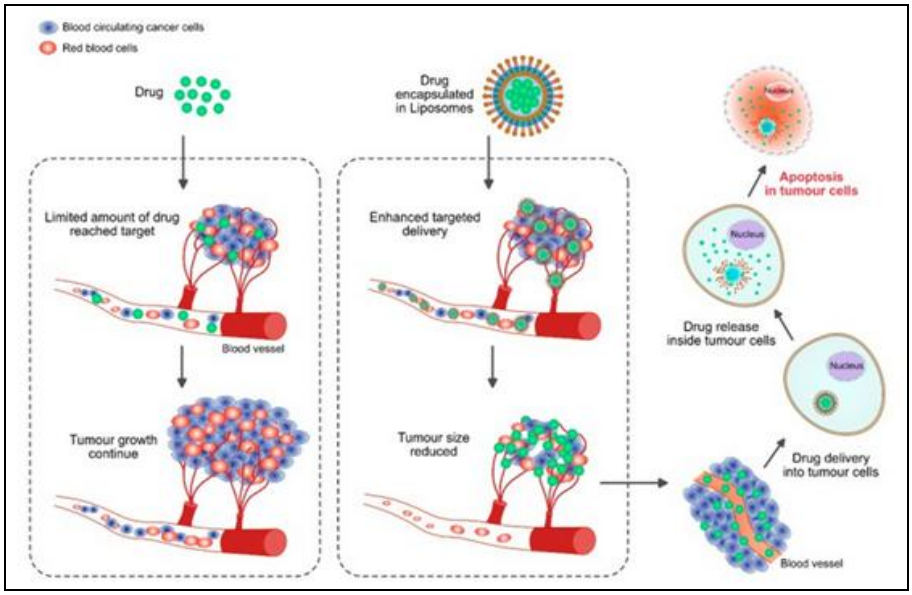

FIG. 5: DRUG DELIVERY WITH AND WITHOUT NANOPARTICLES. NANOPARTICLES-BASED TARGETED DRUG DELIVERY ENHANCED THE ANTITUMOR ACTIVITY DUE TO ENHANCED AND SUSTAINED RELEASE OF DRUG

Recent Advancements in Nanotechnology-Based Formulation for Breast Cancer Therapeutics: NP-based drug-delivery systems have made a remarkable difference in the site-specific release of drugs, especially chemotherapeutic agents, owing to their physical and chemical characteristics and biological attributes [27]. Innovative nanotechnology approaches have become essential for dealing with challenging illness conditions. Consequently, the relevance of promising polymeric nanoparticles strategies for breast cancer therapy has become necessary. The recent applications of polymeric nanoparticles for breast cancer chemotherapeutics are mentioned in **Table 1.**

TABLE 1: OVERVIEW OF THE LATEST RESEARCH IN NANOTECHNOLOGY FOR THE BREAST CANCER

Title of the article	Author	Year	Results	Inference	Refs
Ultrasound triggered herceptin liposomes for breast cancer therapy	Amal Elamir *et al.*	2021	Synthesized immunoliposomes (TRA-liposomes) are within the recommended size (< 200 nm) to benefit from the enhanced permeability and retention (EPR) effect, which allows small particles to extravasate through the leaky vessels surrounding the tumor and accumulate inside the cancerous tissues. Comparison of the performance of free doxorubicin across both cell lines, with and without exposure to low-frequency ultrasound, suggested that liposome to low-frequency ultrasound exposure has a visible effect on the action and uptake of free doxorubicin due to the sonoporation effect.	Scientists stated that overexpression of HER2 receptors on the surface of some breast cancer cells provides a unique platform for HER2-targeted liposomes aiming to deliver their therapeutic to the diseased cells Scientists have successfully synthesized pegylated liposomes and decorated their surfaces with the monoclonal antibody Trastuzumab (TRA-liposomes). They also investigated the effect of applying LFUS (liposomes to low-frequency ultrasound) to stimulate drug release in a controlled manner. In vitro results showed that the combination of Trastuzumab-conjugated liposomes and low-frequency ultrasound is a safe and effective technique in breast cancer treatment.	28

PGMD/ curcumin nanoparticles for the treatment of breast cancer	Mankamna Kumari *et al.*	2021	The size of curcumin nanoparticles 7:3 and curcumin nanoparticles 6:4 were found to be ~ 110 and 218 nm with polydispersity index of 0.174 and 0.36, respectively. Further, the zeta potential of the particles was − 18.9 and − 17.5 mV for curcumin nanoparticles 7:3 and curcumin nanoparticles 6:4, respectively. The entrapment efficiency of both the nanoparticles was in the range of 75–81%	Researchers developed PGMD (polyglycerol-malicacid-dodecanedioic acid)/curcumin nanoparticles-based formulation for anticancer activity against breast cancer cells. The nanoparticles were prepared using both the variants of poly-glycerol-malicacid-dodecanedioic acid polymer with curcumin (i.e. curcumin nanoparticles 7:3 and curcumin nanoparticles 6:4). Though, the polymer PGMD 6:4 is more hydrophilic than PGMD 7:3; there was no significant difference found between the anticancer activities by both the nanoparticle formulations on breast cancer cell lines. Overall, the study showed that the nanoparticles displayed increased anticancer activity than curcumin alone	29
Albumin-Based Nanoparticles for the Delivery of Doxorubicin in Breast Cancer	Rama Prajapathi *et al.*	2021	The Albumin Nanoparticles -N-succinimidyl 3-(2-pyridyldithio) propionate (SPDP) with size of around 156 nm measured by DLS. The release of Doxorubicin from Albumin Nanoparticles -N-succinimidyl 3-(2-pyridyldithio) propionate (SPDP)was highest in tumor-mimicked environments, i.e., with acidic pH and in the presence of glutathione. This is because the Albumin Nanoparticles are cross-linked with disulphide bridges, and hence the higher concentration of glutathione in tumor cells causes destabilization of Albumin Nanoparticles, leading to a higher release of drug.	Scientists used different cross-linking processes and formulated albumin nanoparticles loaded with Doxorubicin to improve the encapsulation efficiency, the in-vitro release of the drug and enhancement of activity in the selected cell lines. The cytotoxicity studies of the Albumin Nanoparticles -N-succinimidyl 3-(2-pyridyldithio) propionate (SPDP) were performed in three different breast cell lines, highlighting the mechanism of cell death. The Doxorubicin encapsulated Albumin Nanoparticles -N-succinimidyl 3-(2-pyridyldithio) propionate (SPDP)showed toxicity in both the breast cancer cells (MCF-7 and MDA-MB-231), but, remarkably, a negligible effect was observed in non-tumoral MCF-10A cells. In addition to the hydrophilic Doxorubicin, this system could be used as a carrier for hydrophobic drugs	30
Novel Chemo Photothermal Therapy in Breast Cancer Using MethotrexateLoaded Folic Acid Conjugated Au@SiO2 Nanoparticles	Reza Agabeigi *et al.*	2020	The zeta potentials of Au@SiO2 (silica-coated gold) nanoparticles were +13.3 mV, which, after dual drug loading, decreased to -19.7 mV in the desirable range. TEM confirmed that Au@SiO2 (silica coated gold) NPs have synthesized with homogenous spherical shape and size was around 25nm	Researchers have designed MTX and FA-loaded Au@SiO2 (silica-coated gold) nanoparticles and found a higher cellular uptake percentage of MDA-MB-231 compared to MCF-7 as two breast cancer cell lines with different folate receptor expression. And found that the combination of chemotherapy and Low level laser therapy improves the potential of breast cancer therapy with minimum side effects	31
Optimization of Docetaxel Loading Conditions in Liposomes: proposing potential products for metastatic breast carcinoma chemotherapy	Roghayyeh Vakili-Ghartavol *et al.*	2020	The sizes of liposomes distributed from 109 nm to 120 nm with a polydispersity index <0.2, implying uniform distribution. Surface morphology in the entire drug loaded NLs were found by TEM to be spherical in shape.*In vivo* experiment with BALB/c mice bearing 4T1 or TUBO breast carcinoma tumors also showed that	In this study, scientists have encapsulated docetaxel in nanoliposomes based on a new remote loading method using mannitol and acetic acid as hydration buffer for the chemotherapy of breast carcinoma. Physicochemical analysis of docetaxel-liposomes revealed that liposomes have appropriate size and zeta potential to target the tumor with enhanced permeability and retention	32

			docetaxel -liposomes could significantly delay tumor growth and prolong the survival time in comparison with control and Taxotere groups at a similar dose of 8 mg/kg.	mechanism. Docetaxel -nanoliposomes were also able to provide prolonged circulation. And they concluded that results could docetaxel delivery and a very low level of drug losing by the liposomes compared to commercially available product	
Therapeutic Potential of Nanoparticle-loaded Hydroxyurea on Proliferation of Human Breast Adenocarcinoma Cell Line	Fateme Azemati *et al.*	2020	The mean size of magnetic iron oxide nanoparticles was 26 nm and the mean size of iron oxide nanoparticles containing Hydroxyurea was determined 48 nm. In both samples, the nanoparticles were observed in a spherical shape with smooth and uniform surfaces. The surface potential of magnetic iron oxide nanoparticles was obtained 3.86mVand pegylated magnetic iron oxide nanoparticles was -29.3 mV.	The results obtained from this study showed that the IC 50 (Inhibitory concentration) level of nanoparticle-loaded Hydroxyurea in combination radiation and hyperthermia on MCF-7 cell line was significantly less than pure Hydroxyurea after 48 h. Also, they have concluded that Hydroxyurea incombination with Fe3O4 nanoparticles induces mitochondrial dependent apoptosis by down regulation of caspase-8. The use of pegylated nanoparticle-loaded Hydroxyurea would be more efficient than using a pure drug.	33
Synthesis and Characterization of Green Zinc Oxide Nanoparticles with Antiproliferative Effects through Apoptosis Induction and MicroRNA Modulation in Breast Cancer Cells	Amir Hossein Aalami *et al.*	2020	The average size of synthesized Zinc oxide nanoparticles was 31.5 nm and was estimated by DLS measurement. Atomic force microscopy (AFM) was employed to recognize the sample's external morphology and roughness. The findings confirmed the significant positive correlation between apoptotic death and nontoxic concentrations of Zinc oxide nanoparticles. Many studies have demonstrated the cytotoxic effect of various metal nanoparticles, including Zinc oxide nanoparticles, on cancer cells.	Scientists stated that the present study showed an eco-friendly synthesis of Zinc oxide nanoparticles using the aqueous leaf extract of *S. officinalis* for the first time. The synthesized Zinc oxide nanoparticles showed potential free radical scavenging capability, which was confirmed by DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis (3 ethylbenzothiazoline-6-sulfonic acid)) assays. Changes in the expression of microRNAs can affect cancer cell viability and behavior and impact on cancer treatment. Compared with other metal oxides, Zinc oxide nanoparticles are simple, low-cost, nontoxic, biosafe, and biocompatible.	34
Triptolide-loaded nanoparticles targeting breast cancer in vivo with reduced toxicity	Wei Zheng *et al.*	2019	The particle size of the nanoparticles was found to be 62 nm, and the zeta potential was +28 mV. Transmission electron microscope (TEM) further confirmed the uniform spheroid structure.The drug loading capacity of triptolide coated with hyaluronic acid nanoparticles was 2.17% and the encapsulation efficiency was 98%.	In the present work, researchers have synthesized nanoformulated triptolide coated with hyaluronic acid (HA) for application in treating breast cancer. The results have shown that triptolide can prevent tumor progression but at the cost of significant toxicity. Based on the results, triptolide coated with hyaluronic acid nanoparticlesin vivo possesses a significant antitumor ability on breast cancer, particularly in the MCF-7 xenograft model. Furthermore, nephrotoxicity and hepatotoxicity could be significantly decreased by TP nanoparticle treatment compared to free triptolide treatment	35
Transferrin-Conjugated Polymeric Nanoparticle for Receptor-Mediated Delivery of	Zar chi Soe *et al.*	2019	The average particle sizes of Doxorubicin/Poloxamer 407&Poloxamer 123 and Doxorubicin / Poloxamer 407&Poloxamer halotranferrin were 72.5 ± 1.5 nm and 90.8 ± 2.1 nm,	In the present study the researchers had developed a transferrin-conjugated polymeric nanoparticle for the targeted delivery of the chemotherapeutic agent doxorubicin in doxorubicin -resistant breast cancer cell lines with minimum	36

Doxorubicin in Doxorubicin-Resistant Breast Cancer Cells			respectively with polydispersity indexes (0.170 ± 0.005 and 0.190 ± 0.004, respectively). TEM images revealed that the NPs had spherical appearance and good size distribution.	toxicity to healthy cells. Transferrin possesses several properties that will be useful for potential therapeutic applications, including small particle size, optimal surface charge to attach to cancer cells, and superior drug loading, while also allowing sustainable, controlled release of doxorubicin. And further the researcher stated that transferrin-targeted NPs can be used as safe and effective drug carriers for the treatment of both doxorubicin -sensitive and -resistant tumors.	
Methotrexate and Curcumin co-encapsulated PLGA nanoparticles as apotential breast cancer therapeutic system: *In-vitro* and *In-vivo* evaluation	Molood Alsadat Vakilinezhad *et al.*	2019	The nanoparticles were prepared by using double emulsion-solvent evaporation method and characterized. The highest drug encapsulation was achieved in methotrexate – curcumin formulation in which methotrexate drug amount curcumin drug amount was 20%	Scientists have fabricated methotrexate and curcumin co-delivery for the treatment of breast cancer, the resulted nanoparticles showed higher cytotoxicity than free methotrexate (MTX) or curcumin (CUR) on the SK-Br-3 cell line. The *in-vivo* results showed the synergistic effect of methotrexate and curcumin co-delivery on inhibiting the progression of breast cancer	37
Engineered polymeric iron oxide nanoparticles as potential drug carrier for targeted delivery of docetaxel to breast cancer cells	Jnanranjan Panda *et al.*	2019	The X-ray diffraction analysis showed good crystallinity of the nanoparticles. The docetaxel-loaded iron oxide nanoparticles (DIONP) showed spherical shape and uniform size distribution in the range of 160–220 nm.	Scientists have developed an optimized PLGA {poly (D, L-lactide-co-glycolic) acid}-based super paramagnetic nanosize carrier of docetaxel for specific delivery of the drug to breast cancer cells. To achieve effective cancer cell penetration and smart RES escape, they fabricated the formulation in the smaller nanosize range (∼200 nm).The present work aimed at formulating a biocompatible iron oxide-docetaxel nano formulation with a potential for magnetically guided breast cancer therapy. The DIONP-1 formulation with a superparamagnetic core, uniform size, satisfactory docetaxel payload, and sustained release profile	38
Starch nanoparticles for delivery of the histone deacetylase inhibitor CG-1521 in breast cancer treatment	Esma Alp *et al.*	2019	Nanoparticles were characterized for particle size and the average particle size of nanoparticles in aqueous solution is 180 nm with a PDI of 0.14.The average zeta potential of void nanoparticles and CG-1521 nanoparticles were −16.1 mV and −10.2 mV respectively	Authors have developed a biocompatible starch nanoparticle formulation of CG-1521, a histone deacetylase inhibitor in preclinical development for hard-to-treat breast cancers, which improves its bioavailability and half-life. However, as free drugs these compounds have limited clinical utility because they are rapidly metabolized in the peripheral circulation. Encapsulating antitumor agents in polymeric NPs has several advantages, including improved drug solubility, protection from systemic metabolism, increased drug exposure time, and reduction of systemic toxicity	39

Zar Chi Soe *et al.* had developed a novel targeted therapy for the chemotherapeutic agent doxorubicin as transferrin (Tf)-conjugated polymeric nanoparticle to overcome the multidrug resistance in cancer therapy. Doxorubicin (Dox), an anthracycline, is considered one of the most powerful chemotherapeutic agents and is commonly used in multiple cancers, including

ovarian and breast cancer. However, the development of drug resistance in cancer cells remains a major hurdle in effective Dox therapy. Three well-known ABC transporters which are responsible for the development of doxorubicin resistance are ABCG2/breast cancer resistance protein (BCRP), ABCB1/p-glycoprotein (P-gp), and ABCC1/multidrug resistance-associated protein 1 (MRP1) [36]. The preparation of transferrin-conjugated polymeric nanoparticles is shown in **Fig. 6.**

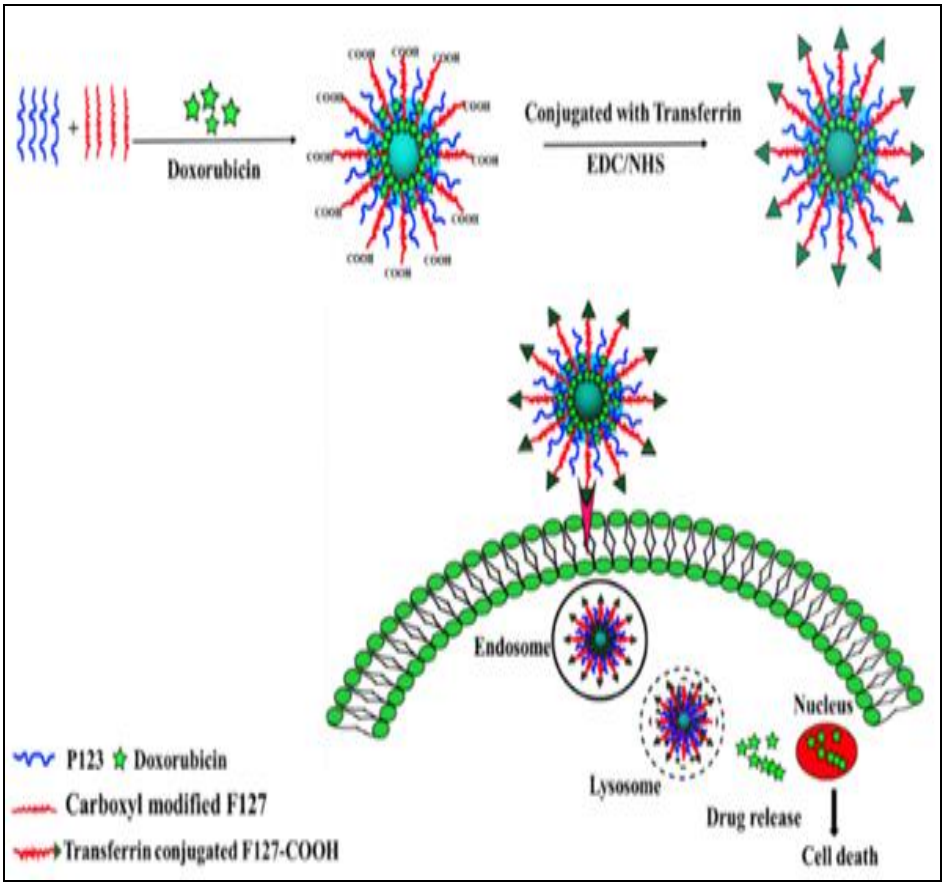

FIG. 6: SCHEMATIC REPRESENTATION OF PREPARATION OF TRANSFERRIN-CONJUGATED POLYMERIC NANOPARTICLE FOR THE RECEPTOR-MEDIATED DELIVERY OF DOXORUBICIN IN DOXORUBICIN-RESISTANT BREAST CANCER CELLS

Doxorubicin F127 & P123 and Doxorubicin F127 & P123-T_f conjugated nanoparticles were prepared by using a modified thin film hydration method with tetra methoxy silane. The prepared nanoparticles were characterized for particle size, polydispersity index (PDI), and zeta-potential of nanoparticles using a dynamic light scattering (DLS) method, including *in-vitro* drug release study, cell migration efficacy, *in-vitro* cell cytotoxicity, *in-vivo* imaging and biodistribution analysis. And the results are reported as below mentioned [36].

TABLE 2: CHARACTERISTIC RESULTS OF THE PREPARED DOXORUBICIN F127 & P123 AND DOXORUBICIN F127 & P123-T_F NANOPARTICLES

Characteristic	Doxorubicin F127 & P123	Doxorubicin F127 & P123-T_f
Particle size	72.5 ± 1.5 nm	90.8± 2.1 nm
Polydispersity index	0.170 ± 0.005	0.190 ± 0.004
Zeta potential	−9.8 ±1.2 mV	-16.5 ± 0.9 mV
TEM	Spherical appearance and good size distribution	Spherical appearance and good size distribution
XRD pattern	More crystalline	Less crystalline
Entrapment Efficiency and Loading Capacity	8.5 ± 4.4% and 22.6 ± 1.2%	95.7 ± 3.7% and 18.5 ± 2.5%

Cell Migration Efficacy of Dox/F127&P123-Tf loaded nanoparticles was carried out by wound healing, and scratch and invasion assays were conducted to assess the progression of cancer cell development in both Dox-sensitive and -resistant cell lines, following treatment with free Doxand formulations with or without Tf-targeting and the results were compared with control [36]. The ability of nanoparticles to induce cell death and apoptosis was evaluated using a live/dead assay in all three cancer cell lines. The accumulation of Dox/F127 & P123-Tf in xenograft mouse models bearing the Tf-recept or expressing Dox-resistant cell line MDA-MB-231(R) was evaluated using an *in-vivo* imaging apparatus and compared to that of cyanine 5.5 loaded non-targeted nanoparticles using an injection model of mice **Fig. 7** [36].

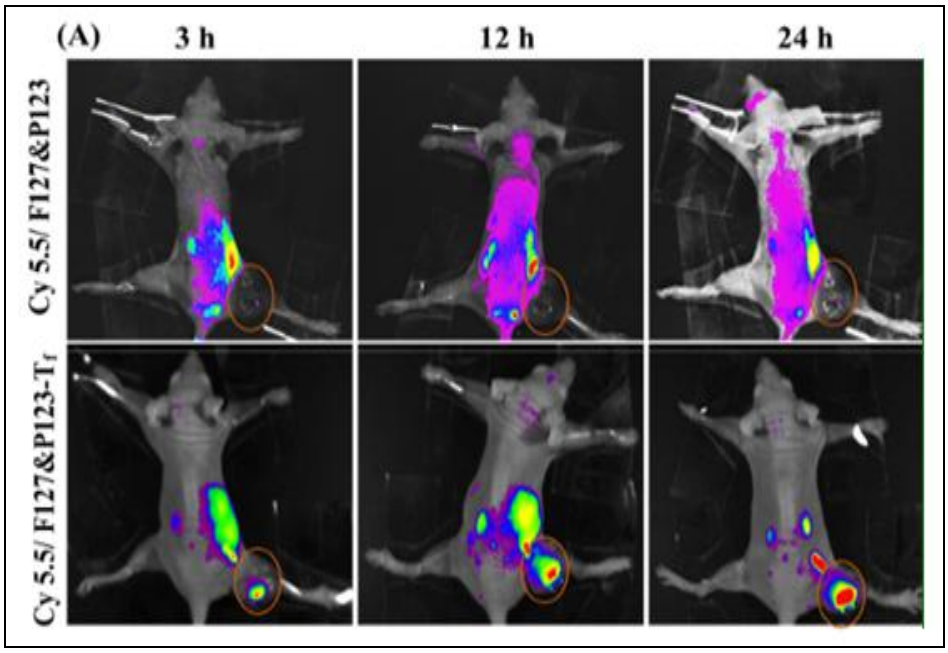

FIG. 7: *IN-VIVO* BIODISTRIBUTION PATTERN OF CYANINE LOADED F127 & P123 AND CYANINE LOADED F127 & P123 -TF IN MDA-MB-231(R) TUMOR-BEARING MICE

The fluorescence intensity of cyanine 5.5 loaded targeted NPs as shown in figure-8, was significantly higher than that of non-targeted NPs and there was minimal ex vivo distribution in the organs examined (heart, liver, spleen, kidney, and lungs) in the targeted NP treatment group. These results supported the successful preparation of a drug delivery system that targets tumor areas and avoids distribution in healthy organs [36]. From all the above-mentioned results it was concluded that the transferrin conjugated doxorubicin nanoparticles possess several properties that will be useful for potential therapeutic applications, including small particle size, optimal surface charge to attach to cancer cells and superior drug loading, while also allowing sustainable, controlled release of Doxorubicin. *In-vitro* data of Dox/F127&P123-Tf treatment in MDA-MB-231(R) suggest that drug resistance can be overcome by the accumulation of doxorubicin in the nuclear region of the cancer cell *via* inhibition of P-gpmediated efflux. In addition, Dox/F127&P123-Tf successfully accumulated in xenograft mouse models bearing the Dox-resistant cell line MDA-MB-231(R), with minimum toxicity to healthy organs. Therefore, Tf-targeted nanoparticles can be used as safe and effective drug carriers for the treatment of both Dox-sensitive and -resistant tumors [36].

Miscellaneous Therapies in Breast cancer:

Conventional Cancer Therapies: The conventional options of treatment for breast cancer include local treatments such as surgery and radiation therapy, which treats the tumor without affecting the rest of the body, and systemic treatments like chemotherapy, endocrine therapy, targeted therapy and immunotherapy, which can reach cancer cells almost anywhere [40]. Surgical resection and chemotherapy are the most common conventional cancer treatments and cure less than 50% of all patients with cancer [41].

Surgical resection is the most effective treatment, with almost 45% of cases cured after the entire or partial removal of affected organs [42]. When not removed, the exposure of malfunctioning organs to chemotherapeutic agents causes damage to rapidly proliferating cells, both neoplastic cells as well as normal cells in the bone marrow, macrophage, digestive tract, and hair follicles. The degree of the side effects enforces the necessity for modification of treatment parameters, such as changes in dosage, in time intervals between repeats, or simply discontinuing the chemotherapeutic program due to the low survival rates after therapy [43].

Combination with Chemotherapy: Co-application of doxorubicin-loaded micelles with imiquimod-loaded micelles was observed to trigger strong CTL responses towards 4T1 orthotropic tumor in mice and significantly diminish tumor growth and metastasis. Liu *et al.* [44] designed a nanomedicine consisting of curcumin (a natural antitumor compound found in the spice turmeric)-loaded polymeric nanoparticles and a nano vaccine containing CpG and antigenic peptides. After injection in 4T1 breast cancer model, this nanomedicine efficiently triggers immunogenic cell death (ICD) of cancer cells and activation of DCs. In addition, the release of immune stimulatory agents from nano vaccine in tumor sites assists in the stimulation of DCs, causing a significant improvement in tumor-specific CD8+T-cell response. This combination induces strong tumor-specific CD8+ T-cell responses that significantly inhibit tumor growth. Together, these studies suggest combining immunotherapy with chemotherapy via nanomedicines offers a strategy for better breast cancer treatment [45].

Combination with photo Thermal Therapy (PTT): In the current popular therapeutic approaches, thermal therapy has grown as a prospective treatment method [46]. Photothermal therapy (PTT) has attracted significant attention as a potentially effective and non-invasive cancer therapy. PTT based on photo-absorbing nanostructures has become different from the general methods [47, 48]. In a typical PTT, that use PTT agents to destroy tumor by getting enough hyperthermia (42°C) under laser irradiation (near-infrared (NIR) light in the range of 700–1100 nm), has been studied as a greatly precise and negligibly invasive method of cancer treatment. This multifunctional nanoparticle was proven to be very effective in eradicating primary tumors and preventing tumor recurrence and metastasis in the 4T1 breast cancer mouse model. Gold nanoparticles have attracted great attention during the past decade due to their high localized surface Plasmon resonance (LSPR) and easy surface conjugation with bimolecular [49]. They have revealed high-performance photo thermal conversion capacity in the NIR area without harmful side effects in biological systems [50].

Combination with Photodynamic Therapy (PDT): Photodynamic therapy (PDT) is becoming a mainstream cancer treatment, receiving tremendous attention in the past decades [51]. PDT is a technique for treating malignant tumors, a modern and non-invasive form of therapy by utilizing harmless light to activate photosensitive chemicals to generate cytotoxic species for malignant cell eradication [52]. First, a drug that absorbs light in the treatment window (650–850 nm), where the tissue is more transparent, is given to the organism. After some time, the target tissue is irradiated. The drug is inactive in the dark; however, electrons generate reactive oxygen species (ROS) locally when it is excited by electrons. It is recognized that induction of cancer cell pyroptosis can remarkably boost the immune system against various tumors.

Recent studies demonstrated that pyroptosis-based chemo- or phototherapy also provides an effective strategy for inhibition of both primary and distant tumor growth [53].

CONCLUSION: Currently available conventional cancer therapeutic strategies suffer from severe limitations such as bio-distribution, insufficient targeting by the therapeutic agents, poor solubility, poor oral bio-availability, low therapeutic indices, dose-limiting toxicity to healthy tissues, and most importantly, almost invariably an emerging drug resistance. Combined with other upgraded therapies, Nanomedicine would be a better alternative for cancer eradication, providing that all the setbacks and clarifications are dealt with. Advanced therapies and emerging techniques in novel drug delivery systems have opened a new era in targeted chemotherapy.

Investigation on nanotechnologies taking root in drug and medical device manufacturing. Novel systems, especially targeted nanoparticles have reduced the prevalence of breast cancer andthe rate of breast cancer–associated morbidity and mortality in recent years. All these studies show that the therapeutic index of many potent anticancer drugs can be improved in solid breast tumors when encapsulated in nanoparticles.

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