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Advances in Nanocarriers for Breast Cancer Treatment: A Comprehensive Review

Mishra S[1], Arti[1], Tiwari A[2] and Mishra B[3]*

[1]Project Associate-I, CDRI, India

[2]Khwaja Moinuddin Chishti Language University, India

[3]Dr. Shakuntala Misra National Rehabilitation University, India

***Corresponding author:** Bharat Mishra, Dr. Shakuntala Misra National Rehabilitation University, Lucknow, India, Email: bharatekansh@gmail.com

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Abstract

Breast cancer (BC) is the most leading disease which is common against women. Its treatment process requires special attention due to disadvantages of conventional methods such as limited therapeutic efficacy, side effects, cytotoxicity, drug resistance and low chances of quality survival. In order to rectify these demerits of conventional system nanocarriers system has been introduced. Various types of nanocarriers such as inorganic and organic polymeric, targeted modified system are used in the nanotreatment of breast cancer. Nanocarriers are the combination of various approached for treating disease. Nanocarriers are able to reduce cytotoxic effect of the anticancer drugs by enhancing cancer cell targeting in contrast to conventional system. This review summarizes broad information about breast and various types of nanocarriers such as polymeric micelles, liposomes (Thermosensitive, Immunoliposomes and pH sensitive liposomes), dendrimer, carbon nanotubes, Nanoparticles(Gold nanoparticles, Mesoporous Silica NPs, PLGA nanoparticles, Metallic nanoparticles, Solid lipid nanoparticles (SLNs), Nanostructured Lipid Carriers (NLC) Silver nanoparticles), Microemulsion, Nanofibers, Carbon dots, Quatum dots, Exosomes, Polymerosomes , Nanoshell , fullerene, hydrogels along with its published research work and application in Breast Cancer Therapy. Paper also emphasizes about the Receptor based drug therapy , Immuno-therapy and Radiation therapy for BC management .This review objects to provide a better understanding of these advancing novel method of cancer treatment and the main issues and key considerations for a rational design of nanocarriers used in combinational delivery of different synergistic anticancer agents.

Keywords: Breast Cancer; Therapy; Receptor; Nanocarriers; Drug Delivery

Abbreviations

NPs: Nanoparticles, BC: Breast Cancer; PTX: Paclitaxel; MTT: 3-(4,5- dimethylthiazol-2-yl)-2-,5- Diphenyltetrazolium Bromide; PHM: postmenopausal hormone therapy; SEM: Scanning Electron Microscopy; TEM: Transmission Electron Microscopy; PTT: Photo Thermal Therapy.

Introduction

Cancer is mainly caused by the mutation in genes which are present in nucleus of all cells in body. Cancer may be benign

or malignant. If cancerous cells remains localized to specific organ of body, it termed as benign tumor however when these tumor cells start migrating towards other organs then it becomes malignant [1]. Being described by six significant trademarks, carcinogenesis might occur in each cell, tissue, and organ, prompting the pathological variations that outcome in countless cancer. The significant instruments that empower its movement incorporate avoidance of apoptosis, boundless ability to isolate, improved angiogenesis, resistance to anti-growth signals and induction of own growth signals, as well as the capacity to metastasize [2].

The number of cancer- related passings is shockingly increasing every year them as one of the considerable reasons for death around the world. Despite the fact that countless cancer doesn't necessarily in every case need to bring about death, they essentially bring down the personal satisfaction and require bigger costs overall Limoni, et al. [3]. As per the invasiveness there are two types of breast cancers- Non-Invasive Breast Cancer cells that are restricted to the pipes and don't attack encompassing fatty and connective tissues of the breast. Ductal carcinoma in situ (DCIS) is the most widely form of non-invasive breast (90%). Lobular carcinoma in situ (LCIS) is less common and considered a marker for expanded breast malignant growth risk. Invasive Breast Cancer cells that break through the duct and lobular wall and invade the surrounding fatty and connective tissues of the breast. Cancer can be invasive without being metastatic (spreading) to the lymph nodes or other organs Mashouri, et al. [4].

There are some specific types of breast cancer that are sub-types of invasive carcinoma. These are much of the time named after features seen when they are seen under the microscope instrument, similar to the manners in which the cells are organized. Some of these may have a better prognosis than standard sensitive ductal carcinoma. These include: Adenoid cystic (or adenocystic) carcinoma, Low-grade adenosquamous carcinoma (this is a type of metaplastic carcinoma), Medullary carcinoma, Mucinous (or colloid) carcinoma, Papillary carcinoma [5].

Breast cancer is a complex disease with multiple factors contributing to its development. Here are some key causes and risk factors associated with breast cancer, over take mutations in certain genes, such as BRCA1 and BRCA2, seriously increase the risk of breast cancer [6]. Women with a family history of breast cancer (especially in first-degree relatives) have a higher risk, The risk of breast cancer growths with age, or if the breast cancer was diagnosed before age 40-45, Breast cancer mainly affects women, although men can also develop it, Early onset of menstruation (before age 12) or late menopause (after age 55) grow the risk, long-standing use of integrate estrogen and progesterone HRT increases breast cancer risk, women who have their first child after age 30 or never have children have a slightly higher, drinking alcohol, even in moderate amounts, is connected with an improved risk, being overweight or obese, especially after menopause, increases the risk. Lack of regular physical activity is a risk factor [7]. Previous radiation therapy to the chest area (for other cancers, for example) increases the risk, Exposure to certain environmental pollutants and chemicals may play a role, though the exact impact is still being studied Vanshikha, et al. [8]. A diet high in saturated fats and low in fruits and vegetables may contribute to an increased risk of breast cancer, women with dense breast tissue have a higher risk of breast cancer, women who have had breast cancer in one breast have an increased risk of developing it in the other breast or a different part of the same breast, Fernández Y, et al. [9] and dietary fat has received the greatest attention. Studies in mice show that high-fat diets increase the frequency and reduce the time to existence of breast cancers. Ω-6 polyunsaturated fatty acids, for example. linoleic acid, are harmful, whereas Ω-3 fatty acids smother human cancer cells implanted in animal models. It has also been suggested that total energy intake is more important than dietary fat. It's important to note that while these factors contribute to the risk of breast cancer, many women who develop breast cancer have no known risk factors other than being female and aging. Regular screenings, early detection, and lifestyle modifications can help reduce the risk and improve outcomes Hani U, et al. [10].

Breast Cancer Risk Factors

Risk factors for breast cancer are as follows it is commonly occur in women over 50 years, women who conceive after the age of 35 have high risk of developing breast cancer. women and men with a family history of breast cancer, especially in a close relative (parent, child, or sibling), are at increased risk for the disease, compared to women without a family history [11]. Various causes of mutation could cause breast cancer risk. Inherited mutations (genetic alterations) in BRCA1 and BRCA2, the most well-studied breast cancer susceptibility genes, account for 5%-10% of all female breast cancers, 5%-20% of male breast cancer, and 15%-20% of all familial breast cancers. High bone mineral density in postmenopausal women has been associated with a 60% to 80% increased risk for breast cancer compared to low bone density [12]. Postmenopausal women with naturally high levels of certain endogenous sex hormones have about twice the risk of developing breast cancer compared to women with the lowest levels [13].

Breast cancer risk increases slightly for each year earlier menstruation begins (by about 5%) and for each year later menopause begins (by about 3%). For example, breast cancer risk is about 20% higher among girls who begin menstruating before age 11 compared to those who begin at

age 13. Likewise, women who experience menopause at age 55 or older have about a 12% higher risk compared to those who do so between ages 50-54 Fornier M, et al. [14]. Breast tissue density is a mammographic indicator of the amount of glandular and connective tissue relative to fatty tissue. Compared to women with 11%-25% breast density, those with 26%-50% or 50% or greater breast density have about 1.6 or 2.3 times, respectively, higher risk of breast cancer [15].

- Novel Drugs Approaches for Breast Cancer
- Organic Drug Delivery Approaches
- Polymeric Micelles

These are colloidal particles prepared from conjugates of water-soluble polymers with phospholipids or long-chain fatty acids and other surfactants. Micelles are used for the delivery of water-insoluble chemotherapeutic drug. Micelles accumulate at poorly vascularized tumors and enhance permeability and retention, and increase the half-life of anticancer agents. They have been shown to overcome P-gp efflux, act through receptor-mediated endocytosis, and increase intracellular drug concentration with enhanced cytotoxicity in MCF-7/ doxorubicin-resistant cells. fabricated immune micelles (antibodies bound to the surface of micelles) were also used in breast adenocarcinomas. Treatment of HER-2-positive breast cancer was performed with antiHER-2 monoclonal antibody (mAb), fabricated with antibody-conjugated lysosomal P (LA-co-TMCC)-g-PEGfuran micelles [16].

Liposomes

Liposomes are classified based on size and composition and influenced by several factors such as bilayered fluidity, surface charge, surface hydration, and methods of preparation. Liposomes have been reported to encapsulate lipophilic and hydrophobic drugs which are stable, nontoxic, biocompatible biodegradable, and non-immunogenic. liposomes are reported to play a role in direct inhibition of P-gp by anionic membrane lipids. Rhodamine retention using P-gp and BCRP substrate in breast cancer. The encapsulation of drugs in liposomes reduces the toxicity through biodistribution. The therapeutic application of liposomes as a drug carrier for the delivery of paclitaxel has also been evaluated in human ovarian cancer The combinations of doxorubicin and cyclophosphamide utilizing non-PEGylated liposomes were used for the treatment of metastatic breast cancer, liposome-conjugated antibody that overexpresses the HER-2 has been developed and reported as delivering 22-fold more calcein to mammary epithelial cells. The synergistic effects of combined drug delivery of quercetin and vincristine through liposomes were reported for treatment of ER-negative breast cancer [17]. Development of liposomes as successful targeted drug delivery systems in breast cancer, they have several advantages listed below Liposomes solubilize lipophilic drugs that would otherwise be difficult to administer intravenously. Liposome encapsulated drugs are inaccessible to metabolizing enzymes; conversely body components (erythrocytes or tissues at the site of injection) are not directly exposed to the full dose of the drug. Liposomes prolong drug action by slowly releasing the drug in the body. Directing potential: Targeting options with liposomes change the distribution of the drug through the body thereby enhancing therapeutic response and reducing the dose of the drug associated toxicity. Since liposomes undergo endocytosis and phagocytosis they can deliver the drugs intracellularly. They can be used to deliver DNA inside the cells hence can work as non-viral transfection systems [18].

Application of Liposomes in Breast Cancer

Vasoactive intestinal peptide receptors grafted sterically-stabilized liposomes for targeted imaging of breast cancer. Liposomes are promising carriers for radionuclide therapy for the following reasons. lipids and cholesterol used for manufacturing of liposome are common constituents of cell membranes and therefore are easily metabolized. liposomes with variable homogeneous particle size ranges can readily be produced by using the extrusion technique, the surface of liposomes can be modified with different kinds of functional groups such as antibodies, proteins, peptides, folic acid, and so forth enabling radio labeled liposomes to be used for molecular imaging and targeted radionuclide therapy, use of different liposome components and different labeling methods to control the liposomes migration and radioisotope release from liposomes may be helpful for delivering a uniform dose distribution in the tumor tissue. Targeted hyperthermia and radiation to the targeted tissues can significantly increase the accumulation of radiolabeled liposomes to targeted tissues . Targeted delivery of radionuclide and therapeutic agents to tumors has important implications for detection, diagnosis, and therapy of cancer. Biomarkers that differentiate cancerous tissue from normal tissues. these attractive molecular targets are vasoactive intestinal peptide receptors (VIP-R), which are over-expressed, about five times, in human breast cancer cells compared to healthy breast tissue [19].

Dendrimers

Dendrimer word was derived from the Greek word dendron which is another name for the tree as it has the same branching in his structure like a tree. Dendrimers are highly branched complex with a core that is symmetrical nature. Dendrimers are in the category of polymer nanoparticles. However, they have a very different structure from classical polymers, which makes them unique. They consist of globular

molecules made out of branched layers (generations). Such a precise synthesis leads to obtaining monodisperse molecules. On their outer surface, dendrimers can be contrived to have various functional sets such as COOH, COONa, NH2, or OH. Therefore, after very simple surface modification, these carriers render smart nanoparticles, transferring sites into specific areas and at the similar time can be used for monitoring. The state of organs attacked by cancer cells, as well as the progress of the curing process. They can help to limit the anti-cancer drug delivery to designed goals only, eliminating many side effects of chemotherapy [20].

The doxorubicin-containing polyion complex micelle accumulates in the nucleus of drug resistant MCF-7 cells and is also considered to have a potent antiproliferative effect on targeted tumor. The cytotoxicity of MCF-7 breast cancer cells. dendrimers–drug conjugate has an antineoplastic agent and is covalently attached to the peripheral groups of the dendrimers, n breast cancer, doxorubicin-G4-PAMAM complexes were encapsulated into the liposomes. These were formulated with HEPC and showed enhanced activity towards the MDA-MB435 breast cells compared to the individual dendrimers. Thus, the methods for delivering the dendrimers-based NPs for transport of drugs into the specific area of malignant cells could be the best approach for delivery of NPs and to treat cancer cells.

Poly-lysine, polypropylene imine (PPI), phosphorus, and carbosilane dendrimers are other forms of dendrimers used in biomedical applications, especially in oncology [21].

Phosphorus Dendrimers

Phosphorus dendrimers proved to be effective in cancer therapy (direct drug carrier and indirect, inducing the apoptosis of cancerous cells) in both forms: alone and functionalized (on the surface with different drugs or metal complexes of dendrimers). Furthermore, phosphorous dendrimers grafted with fluorophores were synthetized and tested in bioimaging. One of the inorganic branching points of dendrimers is the phosphorous-generating the family of “Phosphorhydrazone dendrimers” Dendriplexes were synthetized by complexing small interfering RNA (siRNA) with different cationic dendrimers (phosphorous and carbosilane). The tests performed proved that the most effective siRNA carriers are phosphorus dendrimer [22].

Tryptophan-rich peptide dendrimers

A new type of tryptophan-rich peptide dendrimer (TRPD) has been evaluated in antineoplastic therapy. This dendrimer is extremely effective due to its excellent solubility in water, its highly branched structure with several terminal groups, and generally having a spatial structure similar to proteins. TRPD can interact with intracellular DNA, generating efficient supramolecular aggregates. Furthermore, this dendrimer easily penetrates through the tumor cell membrane, exerting extremely high cytotoxic effects on these cells. In general, this type of dendrimer could obstruct tumor cell proliferation in vivo and lead to tumor cell apoptosis. The dendrimer approach to cancer therapy is promising with regards to improving the effectiveness of treatment [23].

Poly (propylene imine) dendrimers are generally characterized by the e presence of primary amines terminal groups and tertiary propylene amines inside the PPI structure the presence of primary amines terminal groups and tertiary propylene amines inside the PPI structure. The main mechanism by which these dendrimers act is to increase the solubility of the conjugated drug. through electrostatic interactions . The main advantages of these dendrimers include: the ease of surface modification allowing the appearance of high generation dendrimers, as well as the versatility of drug delivery and high functionality [24].

Application of Denderimer in Breast Cancer

In order to be used for their biomedical activity, dendrimers must meet certain conditions, as follows, They must show low toxicity, low immunogenicity, and high permeability, so that they can cross biological barriers, have a proper presence in the systemic circulation and be capable of specific targeting. The limiting characteristic in relation to the medical use of many dendrimers is their cytotoxicity [25].

Carbon Nanotubes

Carbon nanotubes are cylinders made up of one or more co-axial graphite layers with a diameter in the nanometer range that serve as instructive examples of nanomaterials with Janus-like properties. Their structure can be divided into single-walled carbon nanotubes with a single cylindrical carbon wall and multi-walled carbon nanotubes with multiple wall cylinders. They can offer a promising approach to gene and drug delivery for cancer therapy due to their unique electronic, thermal, and structural characteristics. Due to their thermal conductivity and optical properties, carbon nanotubes are the right candidate for killing cancer cells via local hyperthermia. Carbon nanotube materials may be used as instruments for targeted and regulated drug distribution and release, contrast agents for diagnosing and identifying breast tumors, and biosensors.

Developed a folic acid-conjugated raloxifene hydrochloride carbon nanotube for targeting breast cancer cells, and the surface of the CNTs was functionalized by folic acid (FA), allowing the medicine to be delivered selectively to the cancer cells’ target sites., pH can be influenced the drug release. The effectiveness of FAs physically attached to CNTs with affectivity produces apoptosis in the cancer cell [26].

Single-Walled Carbon Nanotube

It is a newer type of nanomaterial possessing unique mechanical, electrical, structural, and optical features which are promising for several biomedical applications, including biosensors, drug delivery transporters and novel biomaterials. In the quest of achieving a specific tumor cells targeting for photothermal ablation, SWNTs was attached to folate for targeting the receptors of folate in folate positive tumor cells or noncovalently conjugated (through adsorption) or indirectly through streptavidin-biotin conjugation to antibodies targeting a specific receptors on the tumor cells. The direct covalent conjugation for specific cancer by targeting antibodies of SWNTs. enhance the pharmacokinetic properties of drugs like Docetaxel, which are insoluble and have low tissue permeability. Needle-like structure of carbon nanotube ease internalization of the biomolecules into the target walled carbon nanotube (SWCNT) [27].

Multiwalled carbon nanotube

They have been reported effective for the administration of several antitumor drugs like topoisomerase I inhibitors, platinum and anti-microtubule drugs, genes, siRNA, immunogenic compounds and aptamers for anticancer treatment. MWNTs are comparatively long, with a cylindrical shaped-nanoparticles whose honeycomb structure produces high surface area relative to their volume, and high porosity. The size of these pores ranges from 4 and 30 nm in diameter. The particles are flexible and durable, comparable to the extracellular matrix (ECM). Because of the importance of cells' physical microenvironment, the ability of MWNT to mimic the normal ECM might be able to modify tumor [28].

- Inorganic Drug Delivery Approaches
- Gold Nanoparticles

GNPs are used in chemotherapy for several cancers. Due to their small size (approximately 130 nm) and specificity, they circulate throughout the tumor cells. GNP coating acts as a biomarker for the cancer diagnosis and is used as a probe for transmission electron microscopy and antimicrobial agents. The conjugation of GNPs to transferrin molecules was tested in breast cancer cells, higher cellular uptake of transferrin molecules bound to GNPs in comparison to unbound molecules. PEG-conjugated liposomes were used for anticancer drug delivery. targeted the breast cancer EGFR/VEGFR-2 signaling pathway using AuNPs-Qu-5, and reported its role in inhibition of migration, invasion, angiogenesis, and metastasis of breast cancer cells and triple-negative breast cancer MDAMB-231 cells were inhibited by phytochemical compounds such as gallic acid capped with GNPs [29].

Mesoporous Silica Nanoparticles

Mesoporous silica NPs (MSNs) have attracted much attention as another inorganic nanomaterial in targeted therapeutic delivery and imaging due to their unique properties such as large surface area, pore volume. and the capability to vary the pore size other than having an easily modifiable surface. MSNs have a high and controllable drug 16 loading capacity due to the characteristic porous surface and are also able to deliver drugs without premature release before reaching the target site, which makes MSNs a good carrier for the easily degradable molecules such as genes and proteins. NPs based DDS of anti-HER2/neu monoclonal antibody [30].

Silver Nanoparticles

SNPs can actuate cytotoxicity on cancer cells and hindering tumor progression without lethality to normal cells and Silver Nanoparticles recommended to development of new anticancer drugs due to broad-spectrum of biological activities Silver Nanoparticles serve as antitumor agents by decreasing progressive development of tumor cells. This might be because of their inhibitory actions in several signaling cascades liable for the development and pathogenesis of cancer [31].

PLGA Nanoparticles

PLGA (poly lactic- co -glycolic acid) is a biodegradable polymer with excellent biocompatibility, and is widely used in the preparation of microspheres, microcapsules, nanoparticles, pellets, implants, and membrane agents. The particle size of PLGA-encapsulated drugs is on a nanometer scale, and thus reduces the adverse reactions of chemotherapy drugs. . PLGA nanoparticles can protect anticancer drugs with low solubility and poor stability in the biological environment. Owing to their small size, they can easy penetrate through capillaries, avoid cellular internalization, and enhance nuclear transport . Also, the surface of the nanoparticles can be modified to allow the targeted delivery of drugs to the tumor cells or other tissues [32].

Metallic nanoparticles

It is static in its metallic state but reacts with the moisture in the skin and the fluid of the wound and gets ionized. The ionized silver is extremely reactive, as it binds to tissue proteins and brings structural changes in the cell wall of bacteria and nuclear membrane leading to cell distortion and cell death. Silver binds to microbial genome (DNA or RNA) by denaturing and inhibits its replication. Silver vessel is also used to make water potable which becomes sterile. As the concentration of Ag+ ion is very low, this has been called oligodynamic action [33].

Application of Metallic Nanoparticles for Breast Cancer Theragnostic

A major barrier that a drug delivery system must be able to avoid in the systemic circulation is the removal

of nanoparticles by phagocytic cells of the mononuclear phagocyte system (MPS). Nanoparticles will usually be taken up by the liver, spleen and other parts of the RES depending on their surface characteristics and undergo opsonisation in the blood and clearance by the RES. In passive targeting, the distribution of nanoparticles is mediated by the MPS's physiological condition. In passive targeting, advantage is taken of the pathological condition of the tumour to allow the accumulation of drug carriers at the target site e pH or specific enzymes present within the tumour cells can be used to facilitate the release of drugs from nanoparticles. Enzymes such as alkaline phosphatase and plasmins are present at a higher level at the tumour site [34]. Active targeting of metallic nanoparticles involves an interaction between peripherally conjugated targeting moiety and a corresponding receptor to facilitate the targeting of a carrier to a specific malignant cell. Drug delivery to the tumour cell can be achieved by means of molecules that are specific to antigens or receptors expressed on the surface of a tumour cell. selecting ligands for receptors on the tumour cell, as ligand--receptor interaction can affect the rate of internalisation, which in turn affects the accumulation of metallic nanoparticles in cancer cells. Therefore, ligands used for receptor targeting in cancer treatment must have the function of inducing receptor-mediated endocytosis (RME) [35].

SPIO-Nanoparticles

Superparamagnetic iron oxides (SPIOs) are used in tissue repair, immunoassay, and for cellular imaging in a magnetic field. They are also used as magnetic resonance contrast agents, controlling the direction of magnetic force to allow monitoring of the physiological and molecular changes in the body. SPIO-NPs have several applications in detection of inflammatory diseases and targeting of surface markers on tumors. SPIO consists of two components, an iron oxide core and a hydrophilic coating of the magnetic particle biomolecule, which allow it to deliver nano-derived biomolecules in a targeted area Biopolymers such as PEG, polyacrylic acid, dextran, alginate, polyethylene imine, and poly (vinyl alcohol) (PVA) are used as coating reagents for the surface stabilization of SPIOs. They bind to tumor sites for delivery of antibodies, enzymes, proteins, drugs, or nucleotides. The uptake of SPIO-loaded PLA-tocopheryl PEG succinate (SPIO-PNPs) by MCF-7 breast cancer cells 8 SPIO-targeted biomarkers have been developed for tumor cell imaging and detection. SPIO-Herceptin detects overexpression of HER-2/neu (c-erbB-2) tyrosine kinase receptor in the metastatic breast cancer. SPIOs most efficiently used in magnetic resonance imaging and macrophage processing. However, knowledge concerning breast cancer and metastatic lymph nodes injection of SPIOs is lacking and needs to be explored. In future, SPIO-NPs could be applied as an effective treatment agent in breast cancer therapy [36].

Solid -Lipid Nanoparticles (SLNs)

SLNs represent a reliable, colloidal drug delivery system, with particle sizes ranging between 10 and 1000 nm. They are based on a natural or synthetic, solid lipid carrier. SLNs are more stable than synthetic polymeric materials, have stable physical and chemical properties, and can overcome the issues with instability. SLNs are of increasing importance, and represents an ideal dosage form that alters drug solubility, allows easier transport to the target, reduces the frequency of administration, and the treatment cost [37].

Estrogen bind to the estrogen receptor it stimulated the normal growth and division of breast tissue cells. Hormonal therapy is the first line of treatment for ER+ breast cancers and Tamoxifen citrate has been the drug of choice for four decades. Tamoxifen citrate belongs to the class of selective estrogen receptor modulators. These selectively bind to the estrogen receptors inhibit the estrogen dependent growth of breast epithelial cells and breast cancer cells [38].

Enhancing Bioavailability of Anti-Breast Cancer Drugs Bioavailability refers to the rate of drug absorption into the bloodstream so that its desired effect becomes available. Although many antitumor drugs for breast cancer have been developed commercially, drug resistance remains a major challenge. MDR lowers drug efficacy through various mechanisms that lead to the ineffective action of drugs on cancer cells. multiple benefits, including lower toxicity and improved stability of the drug, SLNs can overcome the MDR of antitumor drugs [8]. Most side effects of antitumor drugs are caused by damage to normal cells because of the low specificity of the drugs. To overcome this limitation, various methods have been developed to increase the specificity of a drug by conjugating it with a tumor-specific antibody or ligand. SLNs conjugated with hormone receptor-specific antibodies enhance the targeting potential for breast cancer cells [39].

Nanostructured Lipid Carriers (NLCs)

NLCs are the second generation of lipid-based nanocarriers formed from a mixture of solid and liquid lipids and have an unstructured matrix due to the different moieties of the constituents of NLCs. NLCs were designed in order to overcome the SLNs' limitations. NLCs have a higher drug loading capacity because of their imperfect crystal structure and could avoid drug expulsion by avoiding lipid crystallization during the manufacturing and storage periods. NLCs can also increase drug solubility in lipid matrices and they can show more controllable release profiles in comparison to SLNs. NLCs are solid in nature, even in body temperature, they have a lower melting point and, due to their unstructured nature and imperfection in their crystalline behaviors, provide more space for drug

dissolution and payload in the liquid part of the NLC [40].

Formulated a folic acid-loaded curcumin nanostructured lipid carrier using a solvent diffusion approach. The FA-CUR-NLCs were efficient in selective delivery to cancer cells overexpressing FA receptors (FRs). CUR is also delivered to breast cancer cells via FA-CUR-NLCs, boosting anti-tumor action. As a consequence, FA-CUR-NLCs might be a more effective nanomedicine for tumor therapy [41].

Microemulsions

Microemulsions are isotropic, transparent or translucent, thermodynamically stable, oil-water dispersion systems with low viscosity, that are spontaneously formed upon mixing the water phase, an oil phase, a surfactant, and a cosurfactant in specific proportions. Important characteristics, including very low surface tension, small size, high absorption rate, and high permeability. These characteristics not only protect unstable compounds from premature degradation, but also control drug release for improving the bioavailability of drugs. The α-linolenic acid loaded in oil-in-water (O/W) and water-in-oil-in-water (W/O/W) microemulsions inhibited MDA-MB-231 human breast cancer cell proliferation in a dose-dependent manner [42].

Receptor-Based Drug Delivery Approaches

Breast cancer growths are regulated by multiple receptors, and inhibition at the receptor provides a new avenue for cancer therapy and receptors HER-2, EGFR, IGF-IR, and VEGFR, which revealed specific targets for breast cancer cells. HER-2 belongs to EGFR family and is poorly differentiated in triple-negative breast cancer; IGF-IR is regulated by tyrosine kinases, whereas VEGFR works as a stimulus for angiogenesis [43].

HER-2: HER-2 has been reported to be overexpressed in breast cells. It belongs to the EGFR family and strongly correlates with tumorigenesis. Anti-HER-2 therapy using nanocarrier drugs and antibody-directed therapy for the antigen-binding site could be an effective treatment for breast cancer. Blockade of receptor using inhibitors may improve the treatment of trastuzumab-resistant tumors. A tyrosine kinase inhibitor, such as lapatinib, blocks the expression of EGFR (ErbB1) and HER-2 (ErbB2), which are co-expressed in 30% of breast cancers [44].

EGFR: Overexpression of EGFR has been reported in poorly differentiated triple-negative and inflammatory breast cancer cells. There are several members of EGFR family reported, including EGFR (also known as ErbB1 and HER-1), HER-2 (also known as HER-2/neu and ErbB2), ErbB3 (HER3), and ErbB4 (HER4). Out of these, HER-2 was overexpressed in breast cancer. It has been proven that the EGFR expression was correlated with an increased copy number of the gene and protein overexpression in breast cancer. Although drugs including cetuximab, lapatinib, gefitinib, and others have been developed to target the EGFR.

EGFR signaling and the relationship between triple-negative and inflammatory breast cancer-targeted therapies. vascular endothelial growth factor (VEGF), EGFR, Src, and mTOR molecular markers, for the treatments of triple-negative breast cancer, other inhibitors of the PI3K/AKT/mTOR pathway for deregulation in triple negative breast cancer [45].

PARP inhibitors

Poly ADP-ribose polymerase (PARP) inhibitors can block the repair of single-strand breaks in DNA. Mutations in the breast cancer susceptibility (BRCA) gene can cause the loss of double-stranded DNA damage repair function in breast cancer cells . Therefore, PARP inhibitors are used to treat breast cancers carrying mutations in the BRCA gene by simultaneously blocking the repair of single-strand DNA breaks and double-strand DNA damage, leading to the failure of DNA repair and subsequent death of the cancer cells. The synergistic lethal effect of PARP inhibitors and BRCA mutations provides a novel targeted therapy for patients with breast cancer [46].

CDK 4/6 inhibitors

CDK 4/6 is a serine/threonine kinase that regulates the phosphorylation state of the retinoblastoma protein (Rb) by binding to cycling. Phosphorylated Rb releases E2F that activates the expression of a series of genes that participate in DNA replication and cell division, and consequently mediates the G1/S phase transition and progression of the cell cycle. CDK 4/6 plays a central role in tumorigenesis and development, and has emerged as an important molecular target for the clinical management of various tumors. CDK 4/6 plays an essential role in the occurrence and progression of tumors, a series of CDK inhibitors have palbociclib (PD0332991), ribociclib (LEE011), and abemaciclib (LY2835219) . Their mechanism of action involves binding with CDK 4/6-ATP, which inactivates a large population of cyclin D-CDK 4/6 complexes, resulting in the dephosphorylation of the Rb protein. This ultimately results in cell cycle arrest of the tumor cells in the G1 phase, and increased apoptosis [47].

E1A1 gene

The adenovirus type 5E1A protein has been demonstrated to elicit anti-tumor effects through the induction of apoptosis, inhibition of cell cycle progression, induction of differentiated epithelial phenotype, repression of oncogene expression, and sensitization to chemotherapeutic agents and radiation. These unique properties have led to use of

the E1A gene 1 in adenoviral and lipid based gene therapy systems and these systems are best suited for local or intratumor delivery rather than systemic delivery. Because the effective treatment of many primary tumors, as well as metastatic diseases requires systemic delivery systems, a novel gene delivery system. The combination of LPD-E1A1 and paclitaxel is more effective than paclitaxel alone [48].

- Immunotherapy
- Adoptive cell therapy (ACT)

ACT is a promising therapeutic approach for inducing anti-tumor immune responses. In this approach, tumor-specific T, NK, and DC cell. The selected cells in the ACT are mostly functional cytotoxic T lymphocytes (CTLs) that are capable of inducing cytotoxicity instantly following the recognition of specific antigens on the target cell. Various approaches exist for inducing cell death by CTLs, including the secretion of inflammatory cytokines, the expression of Fas ligand (FasL or CD95L or CD178), TRAIL, and the cytotoxic degranulation of perforin and granzyme. In addition to the key role of T cells in antitumor response, NK cells play an inevitable role in eliminating the tumor cells. Promising findings from melanoma, leukemia and neuroblastoma, along with encouraging results from adoptive NK cell therapy in BC [49].

Bispecific antibodies (BiSAbs)

The BiSAbs have been introduced for cancer therapy since the mid 1980s BiSAbs can, independent of the Major Histocompatibility Complex (MHC), activate immune cells such as natural killer (NK) cells, macrophages, and T cells, and simultaneously bind to various antigens, BiSAbs could mediate the interaction between T and tumor cells through activating key molecules such as CD3, subsequently, eliciting T cells against the tumor cells . Additionally, BiSAbs could be applied in BC therapeutic approaches for simultaneously inhibiting more signaling pathways [50].

Cancer vaccines

Vaccines, such as dendritic cell (DC), whole tumor lysate, RNA/DNA, and peptide targeting neoantigen (neoAg) vaccines Nevertheless, cancer vaccine development is regarded as a challenging approach due to limitations in appropriate and relevant antigens for eliciting the immune responses and requirement of the next generation sequencing or developed. And the cancer neoAg vaccines were similar to those of anti-immune checkpoint blockers. Thus, administering a cancer vaccine in combination with other conventional anti-cancer therapeutics or immunotherapy (e.g., immune checkpoints blockade) and for improving vaccine efficacy and safety, including nano/technological approaches for improving neoAgs immunogenicity [51].

Combination Immunotherapy

Due to resistance or poor immune response following immunotherapy, a combination of more than one immunotherapy approach could be beneficial to improve immunotherapy outcomes, trastuzumab (a monoclonal antibody) is the most leading immunotherapy approach in BC, stimulating antibody dependent cellular cytotoxicity. PD-1 is a receptor expressed on activated T cells, and the PD-1/PD-L1 interaction leads to suppression of immune response. Therefore, inhibiting PD L1 on tumor cells could be a beneficial approach; for BC, the PD-1 inhibitor in combination with anti-HER2 CAR T cells resulted in enhanced function and proliferation of T cells [52].

Micelles

Polymeric micelle has attracted increasing attention in treating cancer metastasis and regarded as a promising drug-delivery. Nano-vector polymeric micelle as drug delivery systems was introduced in the first 1990s by Kataoka's group through the preparation of doxorubicin-conjugated block copolymer micelles [53].

These are colloidal particles with size range of 1-100 nm in diameter. These Nano-carriers have composition of surfactants which are composed of two different regions lipophilic tail and hydrophilic head. In aqueous medium these surfactant exist as monomer at low concentration and on enhancing the concentration of surfactant self-assembled aggregation are formed which is known as Micelles. Small micelles have more penetration abilities in solid tumors as they can transport various chemotherapeutic mediators to sites of metastasis after systemic administration, thus promoting their efficacy in suppressing metastasis of different cancer [52].

Polymeric micelle offers an excellent advantage of smaller particle size in contrast to lipid vesicular system. Selection of polymers plays a vital role in the development of micelles, and the selection of polymer for the micelles formation is constructed on the properties of both lipophilic and hydrophilic block polymers. Outer shell of the micelles gives steric stability and inhibits rapid uptake of carrier by reticuloendothelial system (RES) and provides elongated duration of circulation time inside the body [50].

Micelles have been used in delivery of various anticancer agents. Various nanocarriers such as liposomes, nanoparticles and other nanocarriers have been reported for tumour targeting but have several demerits such as development of resistance and poor targeting [46].

Research in Micelle for Breast Cancer

Zheng, et al. [46] developed Calcitriol-Loaded Dual-pH-

Sensitive Micelle (PCDM) which Counteracts Pro-Metastasis Effect of Paclitaxel in Triple-Negative Breast Cancer Therapy. Dual pH sensitive Micelle was developed with calcitriol along with Paclitaxel. At the tumour site Micelle changes its charge from negative to positive and releases Paclitaxel and calcitriol inside the lysosomes because of the structure variation of the polymers composing PCDM under the acidic condition. This property of micelle make them able to escape from mononuclear phagocyte system and easy to target tumour cell [57].

Chu, et al. [51] assembled teniposide loaded micelle for therapy of Breast cancer. Thin film hydration method was employed for development of micelle and prepared micelle was evaluated for different parameters. These results suggested that we have successfully prepared teniposide-loaded MPEG-PCLA micelles with improved safety, hydrophilic and therapeutic efficiency, which are efficient for teniposide delivery. The prepared teniposide micelles may be promising in breast cancer therapy [48].

Resveratrol loaded polymeric micelles was developed by Gregoriou et al for theranostic targeting of breast cancer cells. Drug delivery system made from Pluronic F127 and Vitamin E TPGS were successfully prepared and evaluated for the incorporation of Resveratrol and coumarin 6, developed a fully soluble drug preparation. The resulting nanoparticle was effective at selectively targeting aggressive forms of breast cancer with no significant uptake by immortalized healthy epithelial cells [43]. Liu, et al. [49] developed alendronate modified polymeric micelle for breast cancer. Micelles result in enhanced cytotoxicity, sustained release and improved pharmacokinetic. In animal model treatment micelle attenuated tumorigenesis and significantly enhanced animal lifespan compared to the conventional formulation [40].

Nanoshell: Nanoshell are miniscule structure which are gold coated which are capable of absorbing specific wavelength of light. They have unique property of concentrating at inflammatory and cancer lesion sites through a enhanced permeation and retention process. Nanoshells can be utilized as an alternative nano based carrier for drug delivery systems like molecular conjugates due to their capability for binding to the antigen's revealed surface of a cancer cell [21].

Fay et al fabricated Nanoshell mediated photothermal therapy for chemotherapy in inflammatory breast cancer cells. In this work, we validated our hypothesis using doxorubicin as a model drug and SUM149 inflammatory breast cancer cells as a model cancer subtype. In initial studies, SUM149 cells were exposed to nano-shells and near-infrared light and then stained with ethidium homodimer-1, which is excluded from cells with an intact plasma membrane. The results confirmed that nanoshell-mediated PTT could increase membrane permeability in SUM149 cells. In complementary experiments, SUM149 cells treated with nanoshells, near-infrared light, or a combination of the two to yieldlow-dose PTT were exposed to fluorescent rhodamine 123. Data indicate that nanoshell-mediated PTT is a viable strategy to potentiate the effects of chemotherapy and warrant further investigation of this approach using other drugs and cancer subtypes [32].

Nanofibers: Nanofibers are special nanocarriers due to its unique characteristics of high surface area to volume ratio, suitable mechanical properties (stress, strain, thickness and swelling) ,high porosity with nano-meter dimension and easy production at large scale. Nanofibers are one dimensional compound with diameters 50 nm until 500 nm and length/diameter ratio of more than 1:200 that prepared from polymer solutions or melts. Nanofibers have multi layers, core-shell, ribbon, porous well, necklace-like, web, multi channels, and single layer structures [33].

Sedghi, et al. prepared chitosan nanofiber for treatment of breast cancer recurrence. The results of MTT assay show the prepared nanofibers have excellent anticancer activity against 4T1 breast cancer cells and no cytotoxic effects on the normal cells. Furthermore, these nanofibers are highly effective against both Escherichia coli and Staphylococcus aureus bacteria and show excellent potency to use in suppressing bacterial infections. These results suggest the promising application of the nanofibers for prevention of breast cancer recurrence [14].

Mehnath, et al. fabricated stimuli-responsive polymeric nanofibers encapsulated with an active targeting micellar system for in situ drug delivery. Core–shell nanofibers were prepared using PHM with coaxial electrospinning and distinct core–shell nanofibers formation confirm by SEM and TEM. Nanofibers showed a homogenous distribution of micelles inside the fiber mesh, diffusion, and erosion processes lead to a controlled release of PTX. In vitro drug release and swelling revealed the pH based sustained release of the drug for 180 h from the nanofibers mat. Compared to PTX, drug-loaded nanofibers exhibited higher cytotoxicity for 8 days which was confirmed by the flow cytometry. These promising results confirm, the novel stimuli-responsive core–shell nanofibers actively target breast cancer cells and lead the way to safe cancer therapy [25].

Polymersome: These are artificially made vesicles from the self-assembly of amphiphilic copolymers encompassing an aqueous cavity. Amphilic copolymers consist of hydrophilic and lipophilic. Polymersomes have superior biomedical properties which have greater stability and storage

capabilities and have long circulation time as compared to Liposomes.

Poly-ethyl ethylene, polydimethylsiloxane, Polyethylene, poly acid, poly (ethylene glycol)- b-poly(ε-caprolactone) etc. Polymersomes are stable vesicular structure that encompass the unique ability to load hydrophobic, hydrophilic molecules or the combination of both. Apart from drug delivery they also represent an optimal choice for diagnostic purposes and as tools of imaging. For anticancer therapy, polymersomes can be conjugated with ligands or peptides meant for targeting specific receptors of malignant cells, which in turn helps in reducing off target toxicity and in enhancing the overall therapeutic effect of drug [16].

Additionally, their properties can be altered and can be designed as stimuli responsive polymersomes which proves to be advantageous in chemotherapy of cancer. Owing to these multifaceted characteristics they have fetched the attention of several researchers for solving the problem of solubility and advancing the delivery of taxanes derivative drugs paclitaxel and docetaxel. Although there are numerous limitations related to biosafety and large scale reproducibility that still hampers it use clinically and once these challenges are resolved they can be brought to translational use. This review covers the positive aspects of use of polymersomes as carriers for taxanes drugs along with the results obtained from the experiments performed on different cancer cell lines. It further covers the existing limitations that still needs to be addressed and the future prospects of the use of these vesicular nanostructures in anticancer therapy [27].

Conclusion

This review explores recent advancements in BC diagnosis and treatment, focusing on various nanocarriers such as dendrimers, carbon nanotubes, nanoemulsions, and different types of NPs like polymeric, magnetic NPs, metallic polymerase (such as palladium, platinum, copper, silver, gold, tin oxide, cobalt-doped), lipid-based nanocarriers, micelles, nanobins, and nanobubbles. NPs offer sophisticated and precise targeting of tumors, resulting in increased treatment effectiveness with reduced toxicity. These diverse nanoparticle formulations are currently utilized in therapeutic applications. Ongoing research efforts undertaken by scientists, healthcare professionals, and medical practitioners in the field of nanotechnology are continuously evolving, establishing a robust platform for NPs. In the foreseeable future, nanotechnology is poised not only to expand its role in cancer treatment but also to significantly enhance the landscape of medicine.

Eliminating malignant cells while sparing healthy cells is a crucial component of any anticancer treatment. Breast cancer is the most common cancer in the world and the leading cause of death for women. There are now fewer curative alternatives available for BC patients. Newly developed, highly accurate, and reasonably effective delivery methods, like gene and immunologic therapy, hormone therapy, and radiation therapy, may pave the way for a different approach to the complete eradication of breast cancer.

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