Review Article

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Nanocarriers For Breast Cancer: Advanced Perspective

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ABSTRACT

Breast cancer is the form of cancer most prevalent and intensified progressively among the women population. The propagation of breast cancers takes place in different stages and diagnosed lately. Various approaches have been emerged to treat this clinical condition but these are also integrated with varied side effects. The reason might be attributed to undesired effects of the chemotherapeutic agent and/or haphazard damage to both healthy and cancerous cells. These hitches induce the urge for targeting cancerous cells by the utilization of novel therapeutic platforms. Nano-drug delivery systems are a cluster of different approaches to treating various severe diseases. Henceforward this concept is also applied in the treatment of breast cancer. Nanoparticles exhibits numerous benefits mainly, reduction in dose and low toxicity, solubility enhancement of certain drugs, increased cellular uptake etc. These are the efficient carrier of hydrophobic drugs as these drugs possess challenges in solubility and bioavailability. Cellular uptake by tumor cells is better by nanocarriers owing to a smaller size. The current review is aimed to through light on recent advances in nano-drug targeting in the management of breast cancer.

Keywords: Breast cancer, nanocarriers, nanoparticles.

1. Introduction

Breast cancer is a group of diseases where the breast tissue undergoes mutation and unrestrained multiplication that leads to the formation of lump or mass. Most breast cancers initiate in the lobules (milk glands) or the ducts. Early-stage diagnosis of breast cancer leads to ease of treatment but unfortunately, symptoms are not detected when the mass is small. The most prevalent physical observation of breast cancer is the formation of a hard painless lump that might be enlarged. Some other symptoms include heaviness or pain in the breast, thickening, change in shape, erythema, ulceration, swelling of the breast, nipple changes such as retraction or scaliness, spontaneous discharge from the nipple, especially bloody discharge. Infrequently breast cancer propagates to lymph nodes results in a swelling or lump formation in lymph node [1]. The major reasons for breast cancer are significant family history, genetic predisposition (Abnormal inherited genes *BRCA1* and *BRCA2*), anthropometry (higher weight, weight gain during adulthood and body fat distribution), hormonal causes, lifestyle and dietary causes (alcohol consumption) and environmental reasons (exposure to X-rays) [2].

Breast cancer is categorized as non-invasive and invasive based on site. Briefly, non-invasive cancer is limited to ducts; it is further divided into ductal carcinoma *in-situ* (DCIS) and lobular carcinoma in-situ (LCIS). The former is most common while the latter is rare and lethal. Invasive breast cancer spreads through lobular walls, ducts and invades nearby fatty and connective tissue [3]. Different stages of breast cancer have been segregated as stage 0 to IV depending on tumour, node and metastasis. Stage 0: the disease is confined to the in ducts of the breast tissue and spread in nearby tissue. Stage IA: small tumour, invasive and has not spread to the lymph node. Stage IB: cancer has propagated to lymph nodes; the size is larger than 0.2 mm and smaller than 2 mm. No evidence of tumour in the breast or it may be less than 20 mm or less. Stage IIA: no evidence of tumour in breast or tumour is less than 20 mm but cancer has propagated to 1-3 axillary lymph nodes or tumour is larger than 20 mm but smaller than 50 mm and has not propagated in lymph nodes. Stage IIIA: The cancer of varied size has spread to internal mammary or 4 to 9 axillary lymph nodes but it has restricted in other parts of the body or a tumour bigger than 50 mm, has distended to 1 to 3 axillary lymph nodes. Stage IIIB: The tumour has expanded to the wall of the chest or contributing to ulceration or swelling of the breast or it is detected as inflammatory breast cancer. It may or may not have spread to the internal mammary or up to 9 axillary lymph nodes. It has restricted in other parts of the body. Stage IIIC: A tumour of variable sizes that has expanded to mammary or more than 10 axillary lymph nodes, and/or the lymph nodes under the collarbone. Stage IV (metastatic): The tumour can be of varied size and has been propagated to organs such as the chest wall, lungs, liver, bones, distant lymph nodes, or brain. Frequently, metastatic breast cancer is diagnosed after a previous history of early breast cancer [4].

Breast cancer is the leading cancer death globally, about 57% of the cancer are diagnosed with the advanced stage of breast cancer in India [5] and impacting 2.3 million (2,261,419) population in 159 countries in the year 2020. 684996 women died because of breast cancer in 2020. It is the most widely diagnosed cancer in the majority of countries and the leading cause of cancer death followed by colorectal and lung cancer. Survival rates of breast cancer differ greatly world-wide. The highest mortality rates were found in Western Africa, Melanesia, Micronesia and the Caribbean. Incidence rates of breast cancer are rising fast in South America, Africa, Asia and high-income Asian countries [6].

Various approaches have been developed for the treatment of breast cancer mainly, surgery, radiation therapy, hormonal therapy, immunotherapy and chemotherapy but these suffer from numerous side effects such as loss of appetite, cough, fatigue, nausea, vomiting, diarrhea, constipation, hair loss, mouth sores, nail changes, menstrual changes and fertility issues, cardiomyopathy, neuropathy etc.[7]. These drawbacks necessitate the need to formulate a targeted drug delivery system that will act specifically on cancer cells.

Nanomedicine is an area of nanotechnology; it is associated with the highly precise application of medicine at the molecular level for diagnosis, prevention and treatment of various diseases. Drug delivery systems introduced in the area of nanomedicine ranges from true nanosystems to microparticles in the range of 100 μm. These systems play a vital role in the development of therapeutically active formulations to target various diseases especially cancer [8]. Cancer nanotechnology is a branch of nanotechnology deal-

ing with the application of nanotechnology and nanomaterials approaches for the diagnosis and treatment of cancer. Targeting of the drug through nanotechnology is more favourable, owing to high interstitial fluid pressure, leaky vascular and acidosis. Various benefits of nanotechnology in cancer treatment are investigated that includes locating cancerous tissues in the body, detection of cancer at the premalignant stage, specific targeting of the drug through active or passive targeting, provides controlled release drug delivery, reduction in systemic toxicity, multiple agents could be combined for effective therapy etc. [9]. Targeting can be done through either an active or passive mechanism. Passive targeting is the accumulation of the drug in the tumour owing to enhanced permeability and retention effect as a result of leaky vasculature and impaired lymphatic function [10]. Active targeting denotes the interaction of bio-engineered nano molecule with the cancer cells [11]. Certain chemotherapeutic agents have been evaluated in nanoparticulate formulations. Nanomaterials have been approved by the U.S. Food and Drug Administration (USFDA) for the diagnosis and treatment of breast cancer. Various nanocarrier based approaches for the treatment of breast cancer have been explored in the current review.

2. Nanocarriers in the treatment of breast cancer

Numerous studies have been carried out by using the nanocarriers for the treatment of different types of cancers. Few approaches for the treatment of breast cancers were highlighted in this section.

2.1. Dendrimers

Dendrimers are nano-sized, core-shell nanostructures, radially symmetric with organized homogeneous and monodisperse structures. It resembles tree branches with a diameter ranging from 2-10 nm and synthesized layer by layer [12, 13]. Dendrimers size could be specifically tuned and surface functionality could be modified as per the need. To develop dendrimers for the treatment of breast cancer key properties must be, low polydispersity and the ability to modulate the pharmacokinetics of the drug. The dendrimer composed of Polyamidoamine -drug-trastuzumab conjugates carrying docetaxel or paclitaxel was studied. The dendrimer antibody conjugate was prepared by pH dependant linker and showed extremely high toxicity against the HER-2-(Human epidermal growth factor receptor 2) positive SKBR-3 cells and less toxicity towards HER-2-negative MCF-7 (Michigan cancer foundation-7) cells

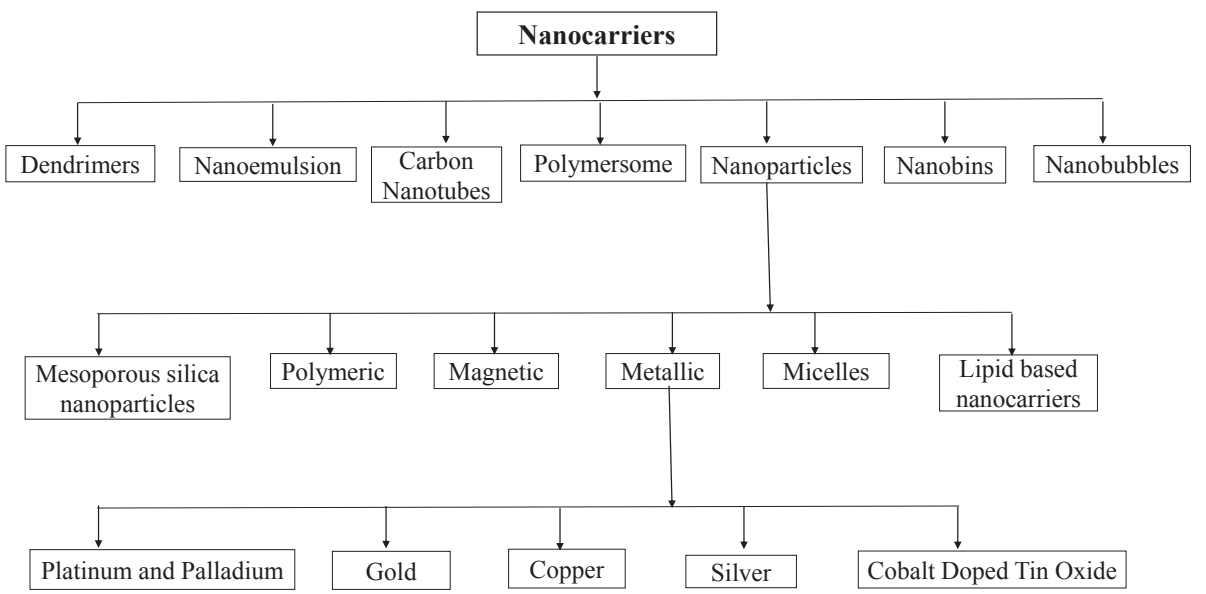

Figure 1. Different nanocarrier based approaches for the treatment breast cancer Dendrimers

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[14]. A similar study was carried out by Kulhari et al (2016), wherein trastuzumab-grafted dendrimers were developed to enhance the delivery of docetaxel against HER2-positive breast cancer cells. *In vitro* studies were suggestive of higher antiproliferation activity and selectivity of targeted dendrimers towards HER2-positive MDA-MB-453 (MD Anderson-Metastatic Breast) human breast cancer cells in comparison with HER2-negative MDA-MB-231 human breast cancer cells. Trastuzumab-grafted dendrimers showed more induction of apoptosis and cellular internalization against MDA-MB-453 cells as compared to unconjugated dendrimers. Conjugation of trastuzumab to the dendrimer surface resulted in site-specific delivery of docetaxel and reduction in systemic toxicity. Besides *in vivo* studies indicated a better pharmacokinetic profile of docetaxel [15]. The fourth generation of poly amidoamine dendrimers with functionalized iron oxide nanoparticles was investigated for Bagg albino strain C mice for the treatment of breast cancer. The formulation was injected intra-tumouraly into Bagg albino strain C mice and then exposed to an alternating magnetic field for 20 min; same process was repeated thrice every other day. The significant destruction of breast cancer cells was found after incubation with dendrimer formulation and exposure to an alternating magnetic field. These results might be attributed to apoptosis and an increase in Bax (Bcl-2 associated X)/Bcl-2(B-cell lymphoma 2) ratio. The inhibition of tumour growth by induction of cancer cell apoptosis and restricted tumour angiogenesis was reported [16]. The efficacy of CXCR4 (C-X-C chemokine receptor) targeted dendrimers carrying doxorubicin was investigated. CXCR4 and its ligand CXCL12 (C-X-C Motif Chemokine Ligand) were responsible for metastasis of different cancer and breast tumours. PAMAM dendrimers composed of doxorubicin were surface-functionalized with CXCR4 recognizable LFC131 (Leave Fare Concession) peptide. The prepared complex was conjugated to breast cancer cells. Enhanced *in-vitro* cytotoxicity with the reduction in infiltration of BT-549-Luc breast cancer cells to chemoattractant was reported [17].

2.2. Nanoemulsion

Emulsions are heterogeneous biphasic liquid dispersed system stabilized with the help of emulsifying agents. Emulsion of nanosize are referred to as nanoemulsions. The size of the nanoemulsion range between 10-1000 nm and is thermodynamically stabilized by a mixture of surfactant and co-surfactant. These were mainly developed to improve the solubility of poorly soluble drugs and avoid first pass metabolism. These had been studieds as carrier for chemotherapeutic agents [18]. Nanoemulsions have the potential to deliver a high concentration of chemotherapeutic agents to cancerous cells. Most of the chemotherapeutic agents are hydrophobic hence exhibited limited solubility in an aqueous solvent; by formulating these drugs in the form of nanoemulsions solubility was proven to be improved. Tuneable size of emulsion facilitates passive targeting by increased retention effect and permeability. Modified nanoemulsions could be long-circulating and utilized for tumour-specific targeting, controlled drug release. Natural compound lapachol is highly effective for diverse biological activities including breast cancer but it's use was restricted due to low solubility and adverse effects. Nanoemulsion of lapachol was developed to enhance bioavailability and protection from degradation. Nanoemulsion was prepared by emulsion phase inversion method and composed of mineral oil, polyoxyethylen-20 sorbitan monolaurate and sorbitan monooleate, medium chain triglycerides, hydrogenated castor oil and sorbitan isostearate. Among the various surfactants; hydrogenated castor oil and sorbitan isostearate were better to form stable emulsion. The formulation was stable after intravenous administration and released the drug in a sustained manner with less toxic effects [19]. Essential oil possesses the anticancer potential against breast cancer without side effects. *Zataria Multiflora* essential oil loaded into chitosan nanoparticles. Nanoparticles were prepared in aqueous solution by mild emulsification and tested against breast cancer cells. The resulting formulation was found to be promising therapeutic and antiproliferative against breast cancer cells [20]. *Nigella sativa* essential oil was formulated in nanoemulsion was found to inhibit the MCF-7 cell viability. It was confirmed by fragmentation of the nucleus, cell membrane blebbing, cytoplasmic vacuolation and marginalization of chromatin. The nanoemulsion induced apoptosis in MCF-7 cells [21]. Nanoemulsion for intraductal administration of a sphingolipid, C6 ceramide that mediates non-apoptotic and apoptotic cell death nanoemulsion was studied. Formulation bioadhesive properties were improved by addition of chitosan. The formulation was found nontoxic against normal cells but showed significant toxicity on MCF-7 cells.

Mammary tissue targeting was enhanced with prolonged localization of the formulation [22].

2.3. Carbon nanotubes

These are tubular carbon allotropes, made up of graphite tubular and diameter ranging from 3-30 nm. These are available as single and multiple-walled with varied properties and methods of synthesis [23]. Single walled nanotubes are prepared by rolling graphene-based nanosheets to form a cylinder having a diameter of 1-2 nm. These are thermally and electrically stable and provide a large surface area owing to these properties, these offers flexibility of attachment of numerous drug and biomolecules and found efficient in cancer diagnosis and treatment [24]. Various anticancer drugs either can be entrapped in the inner cavity or coated on their surface due to large surface area. Surface modified carbon nanotubes exhibit lower toxicity and non-immunogenic [25]. These have ability to cross the plasma membrane and penetrate into cancerous cells [26]. These remarkably restrict cell proliferation and cell adherence; promote the membrane destabilization and rate of oxidative stress. Cytotoxic activity of carbon nanotubes is limited to their purity, length, dimension, concentration and functionalization moieties. Longer nanotubes have less drug loading than shorter ones [27]. Doxorubicin was conjugated via reversible addition-fragmentation chain transfer polymerization with two different end-functionalized poly(1-O-methacryloyl-b-D-fructopyranose-b-(2-methacryloxyethoxy) benzaldehyde glycoblock copolymers by noncovalent or covalent tethering. Further, this product and folic acid were coated on carbon nanotubes separately for dual-targeting of glucose transporter protein and folic acid receptors in breast cancer. The carbon nanotubes were found stable at various physiological conditions. Internalization of doxorubicin was also enhanced along with enhanced anticancer activity and found promising in the treatment of breast cancer [28]. Platinum-based multiple walled carbon nanotubes were developed to load the cisplatin for the treatment of breast cancer and the effect was evaluated using MDA-MB-231 cells. Morphological changes in cells were seen at a higher concentration of cisplatin. The inhibition of apoptosis and absence of DNA damage was seen by suppression of p53, caspase-3 and NF-κB expression in breast cancer cells [29]. To kill cancer cells artemisinin reacts with iron to produce radicals but concomitant delivery of hydrophobic artemisinin and iron is a major hurdle. Multi-walled carbon nanotubes derivatized with hyaluronic acid, targeting ligand transferrin and drug artemisinin was studied on MCF-7 cells. Cytotoxicity of artemisinin was seen due to intracellular accumulation. Synergistic anti-tumour effect of artemisinin and transferrin was observed *in- vitro* on MCF-7 cells and *in-vivo* on tumour-bearing murine model [30]

2.4. Metallic nanoparticles

Metallic nanoparticles exhibited numerous properties such as uniform size and size distribution, high surface to volume ratio, can be modified to allow binding of drugs, ligands and biomolecules, surface plasmon resonance and optical properties. Different nanoparticles have been studied to treat breast cancer.

Gold nanoparticles have been studied for diagnosis, biomedical imaging, and treatment of breast tumours. These can vary in size, shape and structure, easily permeate tumour vasculature, retain in tumours due to the enhanced permeability and retention effect, exhibited physicochemical properties such as the capability to bind with amine and thiol group, flexibility in surface modification and surface plasma resonance [31]. Radiopharmaceuticals can be developed by radiolabelled gold nanoparticles and peptides can be conjugated for better biocompatibility, stability and targeting [32]. Gold nanoparticles were synthesized using a standard citrate reduction technique. Prepared particles were spherical. Anti-ERα antibodies were attached to the gold surface via carbodiimide crosslinking that created an amide bond between the amine group on the antibody and carboxylic acid of a polyethylene glycol molecule. Accumulation of these nanoparticles was studied in MCF-7 cells and found significant internalization within the cells [33]. The activity of collagenase with metformin in conjugation with gold nanoparticles on mammosphere of JIMT-1 breast cell line *in vitro* was studied. Mammospheres treated with the mixture of metformin gold nanoparticles and collagenase gold nanoparticles showed apoptosis and a remarkable reduction in cell prolifereation. Enzymatic modulation of extracellular matrix with collagenase-conjugated nanoparticles might enhance the penetration of chemotherapeutic agents and macromolecules into the solid tumour [34]. Gold nanoparticles were synthesized by naturally derived products such as curcumin, remove the word turmeric, quercetin and paclitaxel.

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Cytotoxic activity of these particles was tested in breast cancer cells, MCF-7 and MDA-MB 231 and all the formulations were found cytotoxic. Combination of all particles showed better activity in terms of inhibiting cell proliferation, colony formation, angiogenesis and apoptosis. Besides, cytotoxicity was not seen in normal cells confirms biocompatibility of formulation [35]. Platinum nanoparticles exhibit thermal stability, better thermal efficiency, hence attracted attention in medicinal application. Platinum nanoparticles and palladium nanoparticles composed of *Gloriosa superba* tuber extract were investigated against triple-negative breast cancer. The resulting nanoparticles showed potent cytotoxicity against MCF-7 cells *in-vitro* [36]. Green synthesis of gold nanoparticles was carried out using leaf extract of *Mimosa pudica* and its anticancer effect in the treatment of breast cancer cell lines was evaluated. The nanoparticles were found to be effective in killing MDA-MB-231 and MCF-7 cells which were confirmed using various anticancer assays. Cell cycle analysis showed apoptosis in G0/G1 to S phase, an increase in tail length was seen in treated cells in comparison with the control revealed in Comet assay, the DNA damage was also reported in treated cells [37]. The surface modification of metallic nanoparticles could enhance the effectiveness and the modification can be done by addition of transition metals like copper, iron and manganese etc. The *Clerodendrum inerme* extract was entrapped in cobalt-doped tinoxide nanoparticles and compared with undoped particles. The co-doped nanoparticles demonstrated remarkable antioxidant activity, significant *in-vivo* antitumor and *in-vitro* anticancer activity on MCF-7 breast carcinoma cells and Ehrlich ascites tumour cell lines respectively. It formulation was found to be biocompatible with lower toxic effects [38]. Silver metal has been widely studied as an antimicrobial agent and nanoparticulate form of silver increases the activity and application of silver. The activity of nanoparticles depends on the surface charge. Positively charged nanoparticles circulated in the blood for prolong period and best suited for cancer application. Nanoparticulate formulation encapsulating vitamin E, catechol within a chitosan matrix and silver nanoparticles synthesized from *Hibiscus rosa- sinensis* petal extracts were studied. The formulation showed better hemocompatibility and encapsulation efficiency. Combined therapy results in targeting with maximum efficiency in MCF-7 cells [39]. Disulfiram has been explored for cancer treatment. Disulfiram entrapped in copper nanoparticles formulated with the 3D printed nanofluidic device was investigated. Disulfiram combines with copper to form the diethyldithiocarbamate copper complex. The formulation had excellent drug loading efficiency, optimum particle size and strong antitumor potential. [40].

2.5. Polymeric nanoparticles

Polymeric nanoparticles are submicron-sized colloidal particles, formulated from biodegradable natural and synthetic polymers. Anticancer drugs are adsorbed, conjugated or encapsulated on or within the polymeric nanoparticles. These are suitable for hydrophilic and hydrophobic drugs and are prepared by a variety of methods. Biodegradable polymers are beneficial due to better encapsulation, higher solubility and permeability and controlled release property. The release of chemotherapeutics agent is taking place by the degradation of the polymeric membrane. Commonly used polymers in the fabrication of polymeric nanoparticles are polylactic-co-glycolic acid, gelatine, albumin, polylactic acid, polyalkyl-cyanoacrylates polycaprolactone and chitosan [41]. Despite various advantages, polymeric nanoparticles suffer from drawbacks such as difficulty in scale-up, polymer cytotoxicity and residual solvent in the formulation [42]. Nanoparticles of poly (lactic-co-glycolic acid) coated with alendronate-modified D-α-tocopheryl polyethylene glycol succinate and folic acid-conjugated D-α-tocopheryl polyethylene glycol succinate were investigated as carrier paclitaxel. The nanoparticles were prepared by single emulsion technique. The formulation showed superior alendronate-mediated binding affinity for hydroxyapatite in bone tissue, promoted uptake by folate receptor-overexpressing cancer cells, promoted cytotoxicity of the drug, restricted lung metastasis and 4T1 tumour growth in treated mice. The destruction and loss of bone in the tumour-bearing mice were significantly hindered and the normal tissues were found to be protected [43]. Redox-sensitive folic acid-conjugated with biodegradable polyether-ester copolymer nanoparticles for concurrent delivery of doxorubicin and indocyanine green (imaging and hyperthermia agent) were developed for combined therapy and simultaneous imaging for breast cancer. Nanoparticles were prepared by thin-film hydration and ultrasonic dispersion technique. The resulting formulation showed synergistic cytotoxic-

ity against mammary cancer cells. The conjugation of folic acid enhanced the accumulation of nanoparticles in EMT-6 breast cancer overexpressing cell lines and laser irradiation enhanced the accumulation of doxorubicin in cancer cells to impart cell toxicity [44]. Active targeting of triple-negative breast cancer was carried out by conjugating the nanoparticles to a peptide that has an affinity to the transferrin receptor. These receptors are overexpressed in triple-negative breast cancer. Benzoporphyrin derivative monoacid (a photosensitizer) was remotely triggered by using near-infrared light and this photodynamic therapy was studied for triple negative breast cancer treatment. Greater fluorescence was seen in actively targeted nanoparticles as compared to passively targeted nanoparticles. The active targeting nanoparticles showed more photo triggered cytotoxicity in cells. Doxorubicin loaded polymeric nanoparticles in polyethylene glycol and hyaluronic acid-ceramide polymer were showed higher cytotoxicity and shelf life as compared to conventional formulations [45]. pH-sensitive polymeric nanoparticles have applications in the delivery of paclitaxel for better therapeutic efficiency. pH-responsive polymers were soluble in acidic pH hence the drug was rapidly distributed and released in the acidic microenvironment of solid breast tumours [46]. Albumin-bound paclitaxel injectable suspension (Abraxane®) has been approved by the FDA in 2005 [47, 48]. Additional studies on nanoparticles were quoted in Table 1.

2.6. Magnetic nanoparticles

Magnetic nanoparticles are a type of nanoparticles in which the activity can be modulated under the influence of an external magnetic field. These are prepared by incorporating magnetic material such as iron, cobalt, nickel and their oxides. These have ability to penetrate cell barriers and concentrated in specific organs or tissue, hence these can be employed for diagnostic as well as the therapeutic purpose [59]. Fluorine-18 labeled arginine–glycine–aspartic acid -coupled ultra-small iron oxide nanoparticles were developed and anti-angiogenic therapeutic potential was tested by dual-modality PET/MRI probe. Studies revealed that larger nanoprobe was accumulated intracellularly and PET in combination with MRI was found more sensitive and precise [60]. Magnetic nanoparticles composed of ferric oxide loaded with tamoxifen and modified by tyrosin were synthesized and anticancer activity was studied on MCF-7 breast cancer cell lines. The formulation showed the cytotoxicity against the cell lines and found it suitable to deliver the tamoxifen [61]. Artemisinin-loaded chitosan magnetic nanoparticles were prepared by ionic gelation method and studied on BALB/c mice model. Formulation exhibited an efficient drug loading and drug encapsulation capacity with the good magnetic property. The particles were effectively accumulated more at blood vessels of cancer tissue [62]. Curcumin-loaded magnetic nanoparticles were prepared by chemical precipitation. The resulting product showed a concentration-dependent internalization in MDA-MB-231 cells. The remarkable anticancer potential was found with nanoparticles in comparison with free curcumin. Moreover, particles showed better magnetic resonance imaging properties and promoted the targeting of curcumin [63].

2.7. Mesoporous silica nanoparticles

Mesoporous silica nanoparticles have a definite structure of internal mesopores with a high volume of pores and surface area. The shape and size of the particles can be modulated as per the requirement. Restriction of premature drug release, more drug loading, surpass multidrug resistance, both passive and active targeting, site-specificity, stimuli-responsive drug release and multifunctional abilities are added advantages of mesoporous nanoparticles [64]. Lactoferrin coupled mesoporous silica nanoparticles were formulated in various stages for phytomedicine ellagic acid and pemetrexed drug release. The particles were of desired size with narrow polydisperbility index and acceptable drug loading efficiency. The hydrophobic ellagic acid was physically trapped within the pores of mesoporous silica by adsorption and electrostatic interaction while pemetrexed was chemically anchored to the lactoferrin shell via chemical conjugation by carbodiimide reaction to restrict early drug release and limit systemic toxicity The faster release of the phytomedicine ellagic acid and the sustained release of pemetrexed was reported by the researcher. The formulation showed maximum cytotoxicity against MCF-7 breast cancer cells [65]. Blocking the pores of silica with stimuli responsive polymers can produce the particles with more precise control over drug release and achieve the target release. pH-responsive mesoporous nanoparticles have been developed as a carrier for anastrozole and then capped with the chitosan-folate conjugate. The hemolysis study confirms the biocom-

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Table 1. Breast cancer delivery by nanoparticles

Drug	Component of drug delivery	Summary	Reference
Paclitaxel	Folic acid Poly(lactic-co-glycolic acid, polyethylene glycol succinate	Accumulation in bone metastases in vivo and retardation of bone destruction and bone loss.	[49]
Quercetin	Poly(lactic-co-glycolic acid, polyethylene glycol 1000 succinate	Tumour growth and metastasis inhibition, restriction in effect on the migration of uPA knockdown MDA-MB231 cells.	[50]
Paclitaxel	polyethylene glycol, folic acid and Superparamagnetic iron oxide	Prolong release of paclitaxel, high drug loading, higher uptake by cancer cells and promoted cytotoxicity.	[51]
Doxorubicin	Lipoic acid, Hyaluronic acid, L-lysine methyl ester	Sufficient restriction of tumour growth, biocompatibility, lesser side effects, targetability and reversal of drug resistance	[52]
Cisplatin	LHRH-modified dextran	Remarkably enhanced the antitumor and antimetastasis efficacy	[53]
Tamoxifen citrate	Polylactide-co-glycolide	Enhanced cytotoxicity than the free drug against MCF-7 breast cancer cells	[54]
Doxorubicin	Chitosan and Pluronic F127	Initial burst release and then sustained release for 24 h. cytotoxicity against MCF-7 cells than the free drug.	[55]
Doxorubicin	Human serum albumin, polyethylenimine	Better cell transfection percentage and cytotoxic effect on MCF-7 breast cancer cells	[56]
Paclitaxel	Albumin	Antitumor activity in a phase II trial in metastatic breast cancer, Phase III study showed nanoparticles exhibit better response rate and time to progression than paclitaxel	[48]
Paclitaxel	Montmorillonite and Poly(D, L-lactide-co-glycolide)	Higher cellular uptake, moderate initial burst followed by a sustained release profile	[57]
Paclitaxel and Ceramide	poly(beta-amino ester) and poly(D,L-lactide-co-glycolide)	Increased tumour accumulation and prolong retention time.	[58]

patibility of the formulation for intravenous use. The nanoparticles exhibited remarkable anticancer activity and tumour-suppressing activity against Ehrlich Ascites Carcinoma induced breast cancer in Balb C mice [66].

2.8. Micelle nanoparticles

Micelles are colloidal dispersions of amphiphilic structures, assembled to form hydrophilic corona and hydrophobic core. These have ability to carry both hydrophilic and hydrophobic drugs. Besides, release of the drug from micelles can be controlled by external stimuli, prolong circulation and stability in blood stream, extended shelf life of drug, structural stability, controlled size distribution, localized in the tumour due to enhanced permeation and retention effect etc. are other advantages of micelles [67]. Certain physicochemical characteristics such as drug loading, nano dimensions, release kinetics and physical stability are of crucial importance before the incorporation of the drug in micelles. Most of the anticancer drugs are hydrophobic such as docetaxel and paclitaxel could be entrapped in the hydrophobic micellar core, besides the solubility of the drug also improve in micellar structure [68]. Zileuton™ -loaded polymeric micelles having antimetastatic and anticancer effects were investigated against *in-vivo* breast cancer stem cell models. The micelles were prepared by thin film hydration technique. The result of the study showed a considerable decrease in cancer stem cells and a remarkable reduction in circulating cancer cells [69]. Hydrophobic drug paclitaxel was bound with poly (ethylene glycol)-block-dendritic polylysine micelles. These were found to exhibit delayed clearance, enhanced tumour accumulation and ultimately enhanced *in-vivo* therapeutic activity in orthotopic human breast cancer xenografts [70]. Docetaxel was encapsulated in monomethoxy poly (ethylene glycol)-poly(ε-caprolactone) micelles and monomethoxy poly (eth-

ylene glycol)-poly(D, L-lactic acid) micelles. Better tumour inhibition was found with micelles entrapping drug as compared to free docetaxel. Acute and genotoxicity studies revealed the micelles were safer to use than injectable docetaxel [71]. Phospholipid-Tween 80 mixed micelles composed of plumbagin were evaluated for sustained release. plumbagin is natural napthaquinnone and highly lipophilic, hence need frequent dosing. Besides, it suffers from severe side effects. These drawbacks drive the entrapment of plumbagin in micelles that improves the bioavailability and reduce side effects along with passive targeting of tumours by enhanced permeation and retention effect. The micelles were prepared from phospholipids (Soayalecithin S80) and Tween 80. About 2.1 fold enhanced antitumour activity was reported by mixed micellar formulation on MCF-7 cells and found safe by intravenous injection [72]. Few examples of polymeric micelles were listed in Table 2.

2.9. Polymersome

These are artificial vesicles produced from the self-assembly of amphiphilic copolymers enclosing an aqueous cavity. These consist of different repeating monomers either branched or chain form. Drug encapsulation and release can be easily modified by various natural and synthetic block copolymers and suitable for hydrophilic and hydrophobic drugs. Various polymers used in polymersome preparation were polyethyl ethylene, polydimethylsiloxane, polyeth-

Table 2. Breast cancer delivery by micelle nanoparticles

Drug	Component of drug delivery	Summary	Reference
Curcumin	Pristine and glucosylated poly(ethylene oxide)-poly(propylene oxide) block copolymers,	glucosylation promoted micellar internalization	[73]
Doxorubicin and Salinomycin	Polyacrylic acid and Polyethylene glycol	Effective for drug-resistant cancer cells and accumulated in MCF-7 and 4T1 cells.	[74]
Paclitaxel	Polyethylene glycol Succinimidyl Succinate	Adherence to the surface of activated platelets and trapped in circulating tumour cells in blood circulation. Promoted metastasis, targeting and penetrating effect via binding with tumour-infiltrating platelets.	[75]
Doxorubicin and Paclitaxel	Lauryl carbamate derivative of plant-based polymer inulin	In-vivo increased circulation time, micelles were more effective than individual drug	[76]
Paclitaxel	Poly (ethylene glycol)-b- poly(lactide)	Increased the intracellular uptake of the drug, with enhanced cytotoxicity and restriction of tumour metastasis on 4T1 cells	[77]
Fisetin	Pluronic127 folic acid	Prolonged circulation, Enhanced bioavailability by 6-fold, plasma elimination was slower with no toxicity.	[78]
Paclitaxel	Dextran-g-indomethacin	Prolong drug release and enhanced cytotoxicity	[79]
Aminoflavone	Anti-epidermal growth factor receptor	Higher accumulation in tumour with no systemic toxicity	[80]
Paclitaxel	PEG-block-poly[(1,4-butanediol)-diacrylate-β-5-amino-1-pentanol] polyethyleneimine-block-PDHA	Selective uptake by tumour cells and satisfactory and quick intracellular drug release.	[81]
Doxorubicin	Biotin and retinoic acid	Cytotoxicity in MCF-7	[82]
Aminoflavone	Poly(amidoamine) dendrimer, poly(ethylene glycol) derivatives	Increased circulation, significant anti-tumour effect	[83]
Doxorubicin	Pluronic copolymer P123 c poly(ethylene glycol)-block-poly (diisopropanolamino ethyl methacrylate) diblock copolymer	Restricts the growth of doxycycline resistant MCF-7/ADR breast cancer	[84]
Paclitaxel	Polyethylene glycol–phosphatidylethanolamine	Better anticancer effect, apoptosis and reduction in tumour cell proliferation in- vitro and in –vivo	[85]

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ylene glycol, polylactic acid, poly(ethylene glycol)-b-poly(ε-caprolactone) etc. [86]. Doxorubicin and gadolinium-based quantum dots were entrapped in poly (ethylene glycol)-poly(ε-caprolactone) nanopolymersomes as theranostic agent. Quantum dots were synthesized from indium-copper-gadolinium-zinc sulphide. Quantum dots and doxorubicin were loaded in polymersome by double emulsion method further investigated as an anti-cancer agent and magnetic resonance-florescence imaging agent. AS1411 DNA aptamer was attached to polymersome for the purpose of targeting. The formulation was stable and released the drug in a controlled manner. Anti-tumour efficacy and diagnostic ability of the formulation was investigated in 4T1 tumour baring mice. Aptamer enhanced the toxicity and cellular targeting in MCF-7 and 4T1 nucleopositive cancer cells lines. [87]. Doxorubicin entrapped in hyaluronan-polycaprolactone polymersome for sustained release and targeting to tumour cells. Doxorubicin was entrapped in hydrophilic compartment of hyaluronan-polycaprolactone polymersomes by nanoprecipitation technique. Hyaluronan cell of the Polymersomes were was responsible for endocytosis and it was confirmed in murine 4T1 and human MCF-7 cancer cell lines. Formulation showed wide bio-distribution, tissue necrosis of tumour and *in-vivo* antitumour potential [88].

2.10. Lipid based nanocarriers

Lipid-based nanocarriers have attracted considerable interest as carriers of drugs with poor oral bioavailability. These offers significant benefits such as low toxicity, ease of scale-up, biocompatibility and high drug loading efficiency etc. Various types of lipid nanocarriers are elaborated below

Liposomes

These are small, spherical-shaped artificial bilayer vesicles prepared from cholesterol and phospholipids. Properties of liposomes can differ based on lipid composition, size, surface charge and preparation method [89]. Liposomes entrapped with metformin alone and conjugated with herceptin were investigated against breast cancer stem cells. Liposomes were prepared by thin film evaporation technique followed by freeze thaw process. Enhanced permeation and retention effects were observed owing to size and surface charge. Liposomes in conjugation with herceptin showed better inhibition of breast cancer stem cells and an immigration effect than free metformin [90]. An additional study carried out with metformin entrapped liposomes. Formulation showed minimum cell migration activity, restricts colony formation and induce apoptosis in breast cancer cells. Enhanced antitumour activity was also reported [91]. Indocyanine green is anionic tricarbocyanine, water-soluble dye used in diagnostic and medical imaging applications. It acts as photosensitizer for photodynamic therapy owing to strong absorption at 805 nm with minimal bioscattering and limited autofluorescence of biomolecules at this wavelength. It was also investigated against triple negative breast cancer. Though it suffers from the drawback of poor pharmacokinetic and short photostability *in vivo*. To improve the circulation of dye near-infrared photodynamic therapy activated thermosensitive liposomes composed of indocyanine green were studied. Liposomes were prepared by thin film extrusion technique. The formulation showed considerable retardation of growth of the tumour, cell viability and enhanced accumulation in tumour in the treatment of triple-negative breast cancer [92]. The first nanomedicine approved by FDA is PEGylated liposome Doxil composed of doxorubicin. It was reported to exhibit extended circulation for up to 55 hours. Tamoxifen (lipophilic drug) and gemcitabine (hydrophilic drug) were loaded in liposomes, having a mean size of 150-200 nm. Both the drugs exhibited a synergistic effect and tamoxifen was found to modulate the release of gemcitabine. 10 fold reduction in the dose of gemcitabine was reported in comparison with commercial GEMZAR formulation [93]. Additional recent studied on liposomes were summarized in Table 3.

Lipid-based nanoparticles

These are applicable for the diagnosis and treatment of breast cancer owing to enhanced permeability and retention effect and flexibility in material selection. Various benefits associated with this delivery are target-specific and superior drug delivery, biodegradable, reduced adverse effects, biocompatible, overcome the solubility and bioavailability problems and reversal of multidrug resistance conditions. By using solid-lipid nanoparticles, the intracellular release of niclosamide for the treatment of triple-negative breast cancer was studied by using MDA-MB231 and TNBC cells. The emulsion solvent evaporation method was used to prepare the solid-lipid nanoparticles and Stearylamin used as principle lipid due to cataionic nature. Cataionic lipids was preferred as it

Table 3. Breast cancer delivery by Liposomes

Drug	Summary	Reference
Doxorubicin	Noteworthy enhanced uptake and efficient targeting of cancer cells in MCF-7 and SKBR-3 cells.	[94]
Daunorubicin and Emodin	Accumulation at tumour tissue, downregulation of few metastasis-related proteins, mainly, MMP-2, VE-cad, TGF-β1 and HIF-1α	[95]
Resveratrol	Encapsulation of drugs within peptide liposomes with the reduction in toxicity.	[96]
Cisplatin	Sustained, thermo-sensitive release, and improved cellular uptake along with cytotoxic effect.	[97]
Paclitaxel	Increased cellular uptake and concentration dependant cytotoxicity against MDA-MB-231 and MCF-7 cells.	[98]
Doxorubicin and Silymarin	Lower concentrations showed synergistic effects for both the drugs	[99]
Epirubicin-hydrochloride	Better growth restriction and the greater percentage of cell death	[100]
Curcumin	Enhanced uptake and higher cytotoxicity.	[101]
A7R-cysteine peptide	Higher accumulation and toxicity in MDA-MB-231 xenografts in vivo.	[102]
Raloxifene	Longer release time, penetration promoting effect of cochleates	[103]
Artemisinin	Enhanced cytotoxic activity due to pegylation	[104]
Thymoquinone	Suppress the proliferation of MCF-7 and T47D breast cancer cell lines with the reduction in toxicity.	[105]

promote the cellular uptake of drug. Tween 80 and pluronic F-68 was used as surfactant. Formulation was optimized by box-behnken design. Cell viability was found to be decreased with increased amount of drug and formulation. Enhancement in intracellular accumulation of the drug and modulation of expression of STAT3, resulted in anticancer potential [106]. Tamoxifen-loaded solid lipid nanoparticles were studied on MCF7 Tam-resistant breast cancer cells (MCF7-TamR) Particles were formulated by the hot homogenization method. Formulation exhibited small particle size and good physical stability. The cytotoxicity results were indicative of intensified effectiveness of tamoxifen and reversal tamoxifen resistance by shifting the levels of expression of specific miRNAs and target genes in both MCF-7 and MCF-7-TamR, encouraging apoptosis without affecting controlled cells [107].

Nanostructured lipid carriers

Second-generation nanocarriers made up of biocompatible lipids, surfactants and co-surfactant are nanostructured lipid carriers. These exhibit high drug loading potential and fewer chances of leakage. Other added benefits are ease of formulation, a modification for controlled release and inhibition of drug degradation [108]. Raloxifene-loaded nanostructured lipid carriers were prepared by ultrasonication method to improve the oral efficacy and reduce the toxicity. Compritol® 888 ATO used as a solid lipid and Transcutol® HP chosen as a liquid lipid. *In vitro* release, studies showed burst release for 4 h and sustained release for 24 h. The formulation showed improved permeability and was found cytotoxic against MCF-7 cells as compared to drug suspension [109]. Multitargeted chemotherapeutic combination of Docetaxel and thymoquinone were delivered by chitosan grafted lipid nanocapsules for the treatment of drug resistance breast cancer. Nanoemulsion technique was used to prepare nanoparticles and ultrasonication and high speed homogenization were employed for further size reduction. The formulation was found to improve the uptake and endosomal escape effect in addition to significant cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cells [110].

2.11. Arsenic trioxide–loaded nanobins

Arsenic is responsible to modulate cellular changes such as induction of apoptosis, stimulation of differentiation, inhibition of proliferation, stimulation of differentiation, and inhibition of angiogenesis [111]. Arsenic trioxide nanobins are nanoparticulate where

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arsenic trioxide is stabilized as nanoscale precipitate inside the pegylated liposome. Nanobins are nanoparticulate core composed of extremely high densities of arsenic and nickel cations. The i*n-vitro* and *in-vivo* activity of novel arsenic trioxide nanobins was studied using breast cancer cells and a mouse model of triple-negative breast cancer. The nanobins were prepared by thin film hydration method with slight modification. The cytotoxicity studies of nanobins were carried out on a panel of human breast cancer cell lines and an immortalized mammary epithelial cell line. Significant improvement in antitumour activity was reported due to the enhancement of pharmacokinetics *in-vivo*, higher tumour accumulation via the enhanced permeation and retention effect and reduced systemic toxicity by shielding healthy tissues [112]. The release of arsenic was triggered at low pH environments approximately 5-6.5. Thus enabled the release of arsenic trioxide inside tumour macrophages, endocytotic vesicles of the tumour and acidic tumour milieu. Nanobins were developed for encapsulating arsenic-based drugs with transition metal ions into liposomes. During the loading, arsenous acid crosses the bilayer membrane in exchange for acetic acid and an insoluble transitional metal such as nickel and cobalt arsenite salt is formed. Formulation was denoted to promote *in-vitro* cytotoxicity as bioactivity was suppressed inside the vesicle. Moreover, these also reduced the systemic toxicity of arsenic trioxide by shielding normal cells due to encapsulation and surpass the drawbacks of free arsenic trioxide. Nanobins were stable for at least 12 months at 4°C with less than10% leakage of free arsenic trioxide [113].

2.12. Nanobubbles

Nanobubbles are long-lasting gas-containing hollow structures in the aqueous solution and exhibit low internal pressure and surface tension due to charged gas/liquid interface. Nanobubbles can be generated when liquid phase subjected phase change by sudden change in pressure below critical value. This phenomenon is known as cavitation. The cavitation is mostly induced by high pressure variations in the flowing liquid or by the passage of ultrasonic wave [114]. A study was carried out for cell-penetrating peptides composed of epidermal growth factor receptor-targeted small interfering RNA nanobubbles for triple-negative breast cancer. Ultrasound-targeted microbubble destruction technology was employed for synergism of nanobubbles. Results showed expression of epidermal growth factor receptor mRNA and protein was effectively down-regulated and breast cancer cell growth was restricted [115]. Hypoxia is common feature of most cancerous cells. The cancer cell survival or death might be affected by hypoxia. Vascular endothelial growth factor is key regulator of angiogenesis, which is found to be induced by hypoxia. Hypoxia contributes to instability of genome due to rapid p53-dependent apoptosis and slowed DNA damage response. One of the strategy to for the treatment of hypoxia is oxygen nanobubbles. The effect of water-containing oxygen nanobubble and air naobubble on breast cancer tumour growth in 4T1-bearing mice was studied. Vascular endothelial growth factor, mRNA expression of p53, cyclin D/Cdk2 and hypoxia-inducible factor genes were measured in the mice. Tumour size, hypoxia-inducible factor gene expression was found significantly reduced, while expression of mRNA was enhanced at the end of treatment for both the nanobubbles [116].

3. Conclusion

Various nanocarriers such as dendrimers, nanoemulsion, nanoparticles, nanomicelles, carbon nanotubes, lipid carriers etc. have been explored for the treatment of breast cancer with the view to deliver the drug along with the reduction in side effects. The key aspects of most of these carriers are targeting and enhancement of cellular uptake of drugs without affecting healthy cells. A detailed understanding of the biological system and mechanism of nano drug delivery systems and could effectively combine to develop more compatible, safe and effective medicine for the treatment of breast cancer. The future scope of nano-formulations is to develop stimuli-responsive formulation for prevention and treatment of breast cancer. Major emphasis should be given on increased clinical trials and scale up of these products in market.

References

1. Breast cancer facts & figures 2019-2020. Atlanta: American Cancer Society, Inc 2019.2019 Available online from: https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: Global Cancer Statistics 2018: GLOBOCAN estimates of

incidence and mortality worldwide for 36 cancers in 185 countries. A Cancer Journal for Clinicians 2018,68:394-424.

3. Sharma GN, Dave R, Sanadya J, Sharma P, Sharma KK: Various types and management of breast cancer: An overview. Journal of Advanced Pharmaceutical Technology and Research 2010,1 (2):109-26.
4. Breast Cancer: Stages. Breast Cancer Guide.2020 Available online from: https://www.cancer.net/cancer-types/breast-cancer/stages
5. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Kondalli LS, Santhappan S, et al.: Cancer statistics, 2020: Report from national cancer registry programme, India. JCO Global Oncology 2020(6):1063-75.
6. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al.: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. A Cancer Journal for Clinicians 2021,0:1-41.
7. Breast Cancer Guide. Breast Cancer: Types of Treatment.2020 Available online from: https://www.cancer.net/cancer-types/breast-cancer/types-treatment
8. Park K: Nanotechnology: What it can do for drug delivery. Journal of Controlled Release 2007,120 (1-2):1-3.
9. Jagdale SC, Shah TP, Kuchekar BS, Chabukswar AR, Baviskar DT: Cancer Nanotechnology. Asian Journal of Pharmaceutics 2009:1-7.
10. Jain RK, Stylianopoulos T: Delivering nanomedicine to solid tumors. Nature Reviews Clinical Oncology 2010,7 (11):653-64.
11. Sapra P, Tyagi P, Allen TM: Ligand-targeted liposomes for cancer treatment. Current Drug Delivery 2005,2 (4):369-81.
12. Srinivasa GS, Yarema KJ: Dendrimers in Cancer Treatment and Diagnosis. In: Kumar CSSR, editor. Nanotechnologies for the Life Sciences, WILEY-VCH Verlag GmbH & Co. ; Weinheim: 2007. pp. 1-43.
13. Kandekar UY, Chaudhari PD, Tambe VS, Vichare VS, Dhole SN: Dendrimers: novel drug nanocarriers. International Journal of Pharmaceutical Sciences and Research 2011,2 (5):1086.
14. Marcinkowska M, Stanczyk M, Janaszewska A, Sobierajska E, Chworos A, Klajnert-Maculewicz B: Multicomponent conjugates of anticancer drugs and monoclonal antibody with PAMAM dendrimers to increase efficacy of HER-2 positive breast cancer therapy. Pharmaceutical Research 2019,36 (11):1-17.
15. Kulhari H, Pooja D, Shrivastava S, Kuncha M, Naidu VGM, Bansal V, et al.: Trastuzumab-grafted PAMAM dendrimers for the selective delivery of anticancer drugs to HER2-positive breast cancer. Scientific Reports 2016,6 (1):23179.
16. Salimi M, Sarkar S, Hashemi M, Saber R: Treatment of breast cancer-bearing balb/c mice with magnetic hyperthermia using dendrimer functionalized iron-oxide nanoparticles. Nanomaterials 2020,10 (11):2310.
17. Chittasupho C, Anuchapreeda S, Sarisuta N: CXCR4 targeted dendrimer for anti-cancer drug delivery and breast cancer cell migration inhibition. European Journal of Pharmaceutics and Biopharmaceutics 2017,119:310-21.
18. Jaiswal M, Dudhe R, Sharma PK: Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech 2015,5:123-7.
19. Mendes Miranda SE, Alcântara Lemos Jd, Fernandes RS, Silva JdO, Ottoni FM, Townsend DM, et al.: Enhanced antitumor efficacy of lapachol-loaded nanoemulsion in breast cancer tumor model. Biomedicine & Pharmacotherapy 2021,133:110936.
20. Salehi F, Behboudi H, Kavoosi G, Ardestani SK: Incorporation of Zataria multiflora essential oil into chitosan biopolymer nanoparticles: A nanoemulsion based delivery system to improve the in-vitro efficacy, stability and anticancer activity of ZEO against breast cancer cells. International journal of biological macromolecules 2020,143:382-92.
21. Periasamy VS, Athinarayanan J, Alshatwi AA: Anticancer Activity of an Ultrasonic Nanoemulsion Formulation of Nigella sativa L. Essential Oil on Human Breast Cancer Cells. Ultrason Sonochem 2016,31:449-55.
22. Migotto A, Carvalho VFM, Salata GC, da Silva FWM, Yan CYI, Ishida K, et al.: Multifunctional nanoemulsions for intraductal delivery as a new platform for local treatment of breast cancer. Drug Delivery 2018,25 (1):654-67.
23. Saifuddin, Raziah NAZ, Junizah AR: Carbonnanotubes: A review on structure and their interaction with proteins. Journal of Chemistry 2013:1-18.
24. De Volder MFL, Tawfick SH, Baughman RH, Hart AJ: Carbon nanotubes: present and future commercial applications. Science 2013,339:535-9.
25. Tajabadi M: Application of carbon nanotubes in breast cancer therapy. Drug Research 2019:1-5.
26. Edgar Pérez-Herrero, Alberto Fernández-Medarde: Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. European Journal of Pharmaceutics and Biopharmaceutics 2015,93:52-79.
27. Dizaji BF, Farboudi A, Rahbar A, Azarbaijan MH, Asgary MR: The role of single- and multi-walled carbon nanotube in breast cancer treatment. Therapeutic Delivery 2020,11 (10).
28. Ozgen PSO, Atasoy S, Kurt BZ, Durmus Z, Yigit G, Dag A: Glycopolymer decorated multiwalled carbon nanotubes for dual targeted breast cancer therapy. Journal of Materials Chemistry B 2020,8 (15):3123-37.

ISSN: 2458 - 8806

29. Badea MA, Prodana M, Dinischiotu A, Crihana C, Ionita D, Balas M: Cisplatin loaded multiwalled carbon nanotubes induce resistance in triple negative breast cancer cells. Pharmaceutics 2018,10 (4):228.
30. Zhang H, Ji Y, Chen Q, Jiao X, Hou L, Zhu X, et al.: Enhancement of cytotoxicity of artemisinin toward cancer cells by transferrin-mediated carbon nanotubes nanoparticles. Journal of Drug Targeting 2015,23 (6):552-67
31. Shukla R, Bansal V, Chaudhary M, Basu A, Bhonde RR, Sastry M: Biocompatibility of gold nanoparticles and their endocytotic fate inside the cellular compartment: a microscopic overview. Langmuir 2005,21 (23):10644-54.
32. Luna-Gutiérrez M, Ferro-Flores G, Ocampo-García BE, Santos-Cuevas CL, Jiménez-Mancilla N, León-Rodríguez D, et al.: A therapeutic system of 177Lu-labeled gold nanoparticles-RGD internalized in breast cancer cells. Journal of the Mexican Chemical Society 2013,57 (3):212-9.
33. Kapara A, Brunton V, Graham D, Faulds K: Investigation of cellular uptake mechanism of functionalised gold nanoparticles into breast cancer using SERS. Chemical Science 2020,11 (22):5819-29.
34. Abdolahinia ED, Nadri S, Rahbarghazi R, Barar J, Aghanejad A, Omidi Y: Enhanced penetration and cytotoxicity of metformin and collagenase conjugated gold nanoparticles in breast cancer spheroids. Life sciences 2019,231:116545.
35. Vemuri SK, Rajkiran RB, Mukherjee S, Uppula P, Gpv S, Reddy GAV, et al.: Novel biosynthesized gold nanoparticles as anti-cancer agents against breast cancer: Synthesis, biological evaluation, molecular modelling studies. Materials Science and Engineering: C 2019,99:417-29.
36. Rokade SS, Joshi KA, Mahajan K, Patil S, Tomar G, Dubal DS, et al.: Gloriosa superba mediated synthesis of platinum and palladium nanoparticles for induction of apoptosis in breast cancer. Bioinorganic Chemistry and Applications 2018,2018.
37. Suganya UKS, Govindaraju K, Prabhu D, Arulvasu C, Karthick V, Changmai N: Anti-proliferative effect of biogenic gold nanoparticles against breast cancer cell lines (MDA-MB-231 & MCF-7). Applied Surface Science 2016,371:415-24.
38. Khan SA, Kanwal S, Rizwan K, Shahid S: Enhanced antimicrobial, antioxidant, in vivo antitumor and in vitro anticancer effects against breast caner cell line by green synthesized undoped SnO2 and Co-doped SnO2 nanoparticles from Clerodendrum inerme. Microbial Pathogenesis 2018,125:366-84.
39. Nayak D, MinzAliva Prity , Ashe S, Rauta PR, Kumari M, chopra P, et al.: Synergistic combination of antioxidants, silver nanoparticles and chitosan in a nanoparticle based formulation: Characterization and cytotoxic effect on MCF-7 breast cancer cell lines. Journal of Colloid and Interface Science 2016,15 (470):142-52.
40. Chang Y, Jiang J, Chen W, Yang W, Chen L: Biomimetic metal-organic nanoparticles prepared with a 3D-printed microfluidic device as a novel formulation for disulfiram-based therapy against breast cancer. Applied Materials Today 2020,18:100492.
41. Kumari A, Yadav SK, Yadav SC: Biodegradable polymeric nanoparticles based drug delivery systems. Colloids and surfaces B: biointerfaces 2010,75 (1):1-18.
42. Du M, Ouyang Y, Meng F, Ma Q, Liu H, Zhuang Y, et al.: Nanotargeted agents: an emerging therapeutic strategy for breast cancer. Nanomedicine 2019,14 (13):1771-86.
43. Chen S-H, Liu T-I, Chuang C-L, Chen H-H, Chiang W-H, Chiu H-C: Alendronate/folic acid-decorated polymeric nanoparticles for hierarchically targetable chemotherapy against bone metastatic breast cancer. Journal of Materials Chemistry B 2020,8 (17):3789-800.
44. Hu C, Fan F, Qin Y, Huang C, Zhang Z, Guo Q, et al.: Redox-sensitive folate-conjugated polymeric nanoparticles for combined chemotherapy and photothermal therapy against breast cancer. Journal of Biomedical Nanotechnology 2018,14 (12):2018-30.
45. Cho H-J, Yoon I-S, Yoon HY, Koo H, Jin Y-J, Ko S-H, et al.: Polyethylene glycol-conjugated hyaluronic acid-ceramide self-assembled nanoparticles for targeted delivery of doxorubicin. Biomaterials 2012,33 (4):1190-200.
46. Potineni A, Lynnb DM, Langerb R, Amiji MM: Poly(ethylene oxide)-modified poly(b-amino ester) nanoparticles as a pH-sensitive biodegradable system for paclitaxel delivery. Journal of Controlled Release 2003,86:223-34.
47. Khanna C, Rosenberg M, Vail DM: A review of paclitaxel and novel formulations including those suitable for use in dogs. Journal of Veterinary Internal Medicine 2015,29 (4):1006-12.
48. Miele E, Spinelli GP, Miele E, Tomao F, Tomao S: Albumin-bound formulation of paclitaxel (Abraxane®ABI-007) in the treatment of breast cancer. International Journal of Nanomedicine 2009,4:99-105.
49. Chen S-H, Liu T-I, Chuang C-L, Chen H-H, Chiang W-H, Chiu H-C: Alendronate/folic acid-decorated polymeric nanoparticles for hierarchically targetable chemotherapy against bone metastatic breast cancer. Journal of Material Chemisry B 2020,8 (17):3789-800.
50. Zhou Y, Chen D, Xue G, Yu S, Yuan C, Huang M, et al.: Improved therapeutic efficacy of quercetin-loaded polymeric nanoparticles on triple-negative breast cancer by inhibiting uPA. Royal Society of Chemistry 2020,10 (57):34517–26 |.
51. Jeon M, Lin G, Stephen ZR, Kato FL, Zhang M: Paclitaxel-loaded iron oxide nanoparticles for targeted breast cancer therapy. Advanced Therapeutics 2019,2 (12):1900081.

52. Zhong Y, Zhang J, Cheng R, Denga C, Meng F, Xie F, et al.: Reversibly crosslinked hyaluronic acid nanoparticles for active targeting and intelligent delivery of doxorubicin to drug resistant CD44+human breast tumor xenografts. ournal of Controlled Release 2015,205:144–54.

53. Li M, Tang Z, Zhang Y, Lv S, Li Q, Chen X: Targeted delivery of cisplatin by LHRH-peptide conjugated dextran nanoparticles suppresses breast cancer growth and metastasis. Acta Biomaterialia 2015,18:132-43.

54. Maji R, Dey NS, Satapathy BS, Mukherjee B, Mondal S: Preparation and characterization of Tamoxifen citrate loaded nanoparticles for breast cancer therapy. International Journal of Nanomedicine 2014,9:3107.

55. Manaspon C, Viravaidya-Pasuwat K, Pimpha N: Preparation of folate-conjugated pluronic f127/chitosan core-shellnanoparticles encapsulating doxorubicin for breast cancer treatment. Journal of Nanomaterials 2012:1-12.

56. Abbasi S, Paul A, Shao W, Prakash S: Nanoparticles for targeted delivery of active agents against tumor cells. Journal of Drug Delivery 2012:1-8.

57. Suna B, Ranganathana B, Fenga S-S: Multifunctional poly(D,L-lactide-co-glycolide)/montmorillonite (PLGA/MMT) nanoparticles decorated by trastuzumab for targeted chemotherapy of breast cancer. Biomaterials 2008,29:475–86.

58. van Vlerken LE, Duan Z, Little SR, Seiden MV, Amiji MM: Biodistribution and pharmacokinetic analysis of paclitaxel and ceramide administered in multifunctional polymer-blend nanoparticles in drug resistant breast cancer model. Molecular Pharmaceutics 2006,5 (4):516–26.

59. Shubayev VI, Pisanic II TR, Jin S: Magnetic nanoparticles for theragnostics. Advanced Drug Delivery Reviews 2009,61 (6):467-77.

60. Wang Y, Liu H, Yao D, Li J, Yang S, Zhang C, et al.: ^{18}F-labeled magnetic nanoparticles for monitoring anti-angiogenic therapeutic effects in breast cancer xenografts. Journal of Nanobiotechnology 2019,17 (1):105.

61. Nosrati H, Rashidi N, Danafar H, Manjili HK: Anticancer activity of tamoxifen loaded tyrosine decorated biocompatible Fe3O4 magnetic nanoparticles against breast cancer cell lines. Journal of Inorganic and Organometallic Polymers and Materials 2018,28 (3):1178-86.

62. Natesan S, Ponnusamy C, Sugumaran A, Chelladurai S, Shanmugam Palaniappan S, Palanichamy R: Artemisinin loaded chitosan magnetic nanoparticles for the efficient targeting to the breast cancer. International journal of biological macromolecules 2017,104:1853-9.

63. Yallapu MM, Othman SF, Curtis ET, Bauer NA, Chauhan N, Kumar D, et al.: Curcumin-loaded magnetic nanoparticles for breast cancer therapeutics and imaging applications. International Journal of Nanomedicine 2012,2 (7):1761-79.

64. Poonia N, Lather V, Pandita D: Mesoporous silica nanoparticles: a smart nanosystem for management of breast cancer. Drug Discovery Today 2018,23 (2):315-32.

65. Ali OM, Bekhit AA, Khattab SN, Helmy MW, Abdel-Ghany YS, Telebab M, et al.: Synthesis of lactoferrin mesoporous silica nanoparticles for pemetrexed/ellagic acid synergistic breast cancer therapy. Colloids and Surfaces B: Biointerfaces 2020,188:110824.

66. Bhavsar D, Gajjar J, Sawant K: Formulation and development of smart pH responsive mesoporous silica nanoparticles for breast cancer targeted delivery of anastrozole: In vitro and in vivo characterizations. Microporous and Mesoporous Materials 2019,279:107-16.

67. Mukherjee B, Chakraborty S, Mondal L, Satapathy BS, Sengupta S, Dutta L, et al.: Multifunctional drug nanocarriers facilitate more specific entry of therapeutic payload into tumors and control multiple drug resistance in cancer. In: Grumezescu AM, editor. Nanobiomaterials in Cancer Therapy, William Andrew Publishing: 2016. pp. 203-51.

68. Cho H, Lai TC, Tomoda K, Kwon GS: Polymeric micelles for multi-drug delivery in cancer. AAPS PharmSciTech, 2015,16 (1):10-20.

69. Gener Paea: Zileuton™ loaded in polymer micelles effectively reduce breast cancer circulating tumor cells and intratumoral cancer stem cells. Nanimedicine: Nanotexhnology Biology and Medicine 2020,24:102106

70. Xiang J, Wu B, Zhou Z, Hu S, Piao Y, Zhou Q, et al.: Synthesis and evaluation of a paclitaxel-binding polymeric micelle for efficient breast cancer therapy. Science China Life Sciences 2018,61 (4):436-47.

71. Tan L, Ma B, Chen L, Peng J, Qian Z: Toxicity evaluation and anti-tumor study of docetaxel loaded mPEG-polyester micelles for breast cancer therapy. Journal of Biomedical Nanotechnology 2017,13 (4):393-408.

72. Bothiraja C, Kapare HS, Pawar AP, Shaikh KS: Development of plumbagin-loaded phospholipid–Tween®80 mixed micelles: formulation, optimization, effect on breast cancer cells and human blood/serum compatibility testing. Therapeutic Delivery 2013,4 (10):1247–59.

73. Lecot N, Glisoni R, Oddone N, Benech J, Fernández M, Gambini JP, et al.: Glucosylated polymeric micelles actively target a breast cancer model. Advanced Therapeutics 2021,4 (1):2000010.

74. Cui Y, Yang Y, Ma M, Xu Y, Sui J, Li H, et al.: Reductive responsive micelle overcoming multidrug resistance of breast cancer by co-delivery of DOX and specific antibiotic. Journal of Material Chemisry B 2019,7 (40):6075-86.

ISSN: 2458 - 8806

75. Zhang Y, Zhu X, Chen X, Chen Q, Zhou W, Guo Q, et al.: Activated platelets-targeting micelles with controlled drug release for effective treatment of primary and metastatic triple negative breast cancer. Advaced Functional Materials 2019,29 (13):1806620.
76. Kesharwani SS, Dachineni R, Bhat GJ, Tummala H: Hydrophobically modified inulin-based micelles: Transport mechanisms and drug delivery applications for breast cancer. Journal of Drug Delivery Science and Technology 2019,54:101254.
77. Wang J, De G, Yue Q, Ma H, Cheng J, Zhu G, et al.: pH Responsive Polymer Micelles Enhances Inhibitory Efficacy on Metastasis of Murine Breast Cancer Cells. Frontiers in Pharmacology 2018,9 (543).
78. Pawar A, Singh S, Rajalakshmi S, Shaikh K, Bothiraja C: Development of fisetin-loaded folate functionalized pluronic micelles for breast cancer targeting. Artif Cells Nanomed Biotechnol 2018,46 (sup1):347-61.
79. Ji W, Wang B, Fan Q, Xu C, He Y, Chen Y: Chemosensitizing indomethacin-conjugated dextran-based micelles for effective delivery of paclitaxel in resistant breast cancer therapy. PLoS ONE 2017,12 (7):0180037.
80. Wang Y, Wang Y, Chen G, Li Y, Xu W, Gong S: Quantum-dot-based theranostic micelles conjugated with an anti-EGFR nanobody for triple-negative breast cancer therapy. ACS Applied Materials & Interfaces 2017,9 (36):30297-305.
81. Tang S, Meng Q, Sun H, Su J, Yin Q, Zhang Z, et al.: Dual pH-sensitive micelles with charge-switch for controlling cellular uptake and drug release to treat metastatic breast cancer. Biomaterials 2017,114:44-53.
82. Hassanzadeh F, Varshosaz J, Khodarahmi GA, Rostami M, Hassanzadeh F: Biotin-encoded pullulan-retinoic acid engineered nanomicelles: Preparation, optimization and in vitro cytotoxicity assessment in MCF-7 cells. Indian Journal of Pharmaceutical Sciences 2016,78 (5):557-65.
83. Brinkman AM, Chen G, Wang Y, Hedman CJ, Sherer NM, Havighurst TC, et al.: Aminoflavone-loaded EGFR-targeted unimolecular micelle nanoparticles exhibit anti-cancer effects in triple negative breast cancer. Biomaterials 2016,101:20-31.
84. Yu H, Cui Z, Yu P, Guo C, Feng B, Jiang T, et al.: pH-and NIR light-responsive micelles with hyperthermia-triggered tumor penetration and cytoplasm drug release to reverse doxorubicin resistance in breast cancer. Advanced Functional Materials 2015,25 (17):2489-500.
85. Wang T, Yang S, A. ML, Parmar CK, Gillespie JW, Praveen KP, et al.: Paclitaxel-loaded peg-pe–based micellar nanopreparations targeted with tumor-specific landscape phage fusion protein enhance apoptosis and efficiently reduce tumors. Molecular Cancer Therapeutics 2014,13 (12):2864-75.
86. Zhang X-y, Zhang P-y: Polymersomes in Nanomedicine - A Review Current Nanoscience 2017,13:124-9.
87. Zavvar T, Babaei M, Abnous K, Taghdisi SM, Nekooei S, Ramezani M, et al.: Synthesis of multimodal polymersomes for targeted drug delivery and MR/fluorescence imaging in metastatic breast cancer model. International Journal of Pharmaceutics 2020,578:119091.
88. Shahriari M, Taghdisi SM, Abnous K, Ramezani M, Alibolandi M: Synthesis of hyaluronic acid-based polymersomes for doxorubicin delivery to metastatic breast cancer. International Journal of Pharmaceutics 2019,572:118835.
89. Abolfazl Akbarzadeh, Rogaie Rezaei-Sadabady, Soodabeh Davaran, Sang Woo Joo, Nosratollah Zarghami, Younes Hanifehpour, et al.: Liposome: classification, preparation, and applications. Nanoscale Research Letters 2013,8:102.
90. Lee J-Y, Shin DH, Kim J-S: Anticancer effect of metformin in herceptin-conjugated liposome for breast cancer. Pharmaceutics 2020,12 (1):11.
91. Shukla SK, Kulkarni NS, Chan A, Parvathaneni V, Farrales P, Muth A, et al.: Metformin-encapsulated liposome delivery system: an effective treatment approach against breast cancer. Pharmaceutics 2019,11 (11):559.
92. Shemesh CS, Moshkelani D, Zhang H: Thermosensitive liposome formulated indocyanine green for near-infrared triggered photodynamic therapy: In vivo evaluation for triple-negative breast cancer. Pharmaceutical Research 2015,32:1604–14.
93. Coscoa D, Paolinoa D, Cilurzoa F, Casalea F, Frestaa M: Gemcitabine and tamoxifen-loaded liposomes as multidrug carriers for the treatment of breast cancer diseases. International Journal of Pharmaceutics 2012,422:229– 37.
94. Chowdhury N, Chaudhry S, Hall Nea: Targeted delivery of doxorubicin liposomes for HER-2+ breast cancer treatment. AAPS PharmSciTech 2020,21 (202).
95. Fu M, Tang W, Liu J-J, Gong X-Q, Kong L, Yao X-M, et al.: Combination of targeted daunorubicin liposomes and targeted emodin liposomes for treatment of invasive breast cancer. Journal of Drug Targeting 2020,28 (3):245-58.
96. Zhao YN, Cao YN, Sun J, Liang Z, Wu Q, Cui SH, et al.: Anti-breast cancer activity of resveratrol encapsulated in liposomes. Journal of Material Chemisry B 2020,8 (1):27-37.
97. Ghafari M, Haghiralsadat F, Khanamani S, pour F, Reza JZ: Development of a novel liposomal nanoparticle formulation of cisplatin to breast cancer therapy. Journal of Cellular Biochemistry 2020,121 (7):3584-92.
98. Okamoto Y, Taguchi K, Imoto S, Chuang VTG, Yamasaki K, Otagiri M: Cell uptake and anti-tumor effect of liposomes containing encapsulated paclitaxel-bound albumin against breast

cancer cells in 2D and 3D cultured models. Journal of Drug Delivery Science and Technology 2020,55:101381.

99. Gheybi F, Alavizadeh SH, Rezayat SM, Zendedel E, Jaafari M: Chemotherapeutic activity of Silymarin combined with doxorubicin liposomes in 4T1 breast cancer cells. Nanomedicine Research Journal 2019,4 (1):29-34.

100. Alexander P, Jainamboo M, Praseetha PK, Gopukumar ST: Silica coated liposomes for drug delivery towards breast cancer cells. Rasayan Journal of Chemistry 2016,9 (3):300 - 8.

101. Jadia R, Kydd J, Piel B, Rai P: Liposomes aid curcumin's combat with cancer in a breast tumor model. Oncomedicine 2018,3:94-109.

102. Cao J, Wang R, Gao N, Li M, Tian X, Yang W, et al.: A7RC peptide modified paclitaxel liposomes dually target breast cancer. Biomaterials Science 2015,3 (12):1545-54.

103. Ağardan NBM, Değim Z, Yılmaz Ş, Altıntaş L, Topal T: The effectiveness of raloxifene-loaded liposomes and cochleates in breast cancer therapy. AAPS PharmSciTech 2016,17 (4):968-77.

104. Dadgar N, Esfahani MKM, Torabi S, Alavi SE, Akbarzadeh A: Effects of nanoliposomal and pegylated nanoliposomal artemisinin in treatment of breast cancer. Indian Journal of Clinical Biochemistry 2014,29 (4):501-4.

105. Odeh F, Ismail SI, Abu-Dahab R, Mahmoud IS, Bawab AAl: Thymoquinone in liposomes: a study of loading efficiency and biological activity towards breast cancer. Drug Delivery 2012,19 (8):371-7.

106. Pindiprolu SKSS, Chintamaneni PK, Krishnamurthy PT, Ganapathineedi KRS: Formulation-optimization of solid lipid nanocarrier system of STAT3 inhibitor to improve its activity in triple negative breast cancer cells. Drug Development and Industrial Pharmacy 2019,45 (2):304-13.

107. Guney EG, Cecener G, Dikmen G: Solid lipid nanoparticles: reversal of tamoxifen resistance in breast cancer. European Journal of Pharmaceutical Sciences 2018,120:73-88.

108. Mehnert W, Mader K: Solid lipid nanoparticles: production, characterization and applications. Advance Drug Delivery Review 2001,47:165-96.

109. Soni NK, Sonali LJ, Singh A, Mangla B, Neupane YR, Kohli K: Nanostructured lipid carrier potentiated oral delivery of raloxifene for breast cancer treatment. Nanotechnology 2020,31 (47):475101.

110. Zafar S, Akhter S, Ahmad I, Hafeeze Z, Rizvi MAM, Jain GK, et al.: Improved chemotherapeutic efficacy against resistant human breast cancer cells with co-delivery of Docetaxel and Thymoquinone by Chitosan Grafted Lipid Nanocapsules: Formulation optimization, in vitro and in vivo studies. Colloids and Surfaces B: Biointerfaces 2020,186:110603.

111. Miller WHJ, Schipper HM, Lee JS, Singer J, Waxman S: Mechanisms of action of arsenic trioxide. Cancer Research 2002,62:3893–903.

112. Ahn RW, Chen F, Chen H, Stern ST, Clogston JD, Patri AK, et al.: A novel nanoparticulate formulation of arsenic trioxide with enhanced therapeutic efficacy in a murine model of breast cancer. Clinical Cancer Research 2010,16 (14):3607-17.

113. Chen H, MacDonald RC, Li S, Krett NL, Rosen ST, O'Halloran TV: Lipid encapsulation of arsenic trioxide attenuates cytotoxicity and allows for controlled anticancer drug release. Journal of american Chemical Society 2006,128:13348-9.

114. Agarwal A, Ng WJ, Liu Y: Principle and applications of microbubble and nanobubble technology for water treatment. Chemosphere 2011,84 (9):1175-80.

115. Hui J, Wen C, Shouqiang L, Bolin W, Xiaoping L, Shouping X, et al.: Novel cell-penetrating peptide-loaded nanobubbles synergized with ultrasound irradiation enhance EGFR siRNA delivery for triple negative Breast cancer therapy. Colloids and Surfaces B: Biointerfaces 2016,146:387–95.

116. Mahjour A, Khazaei M, Nourmohamadi E, Sarkarizi HK: Evaluation of antitumor effect of oxygen nanobubble water on breast cancer-bearing BALB/c mice. Journal of Cellular Biochemistry 2019,120 (9):15546-52.

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