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A Systemic Review of Polymeric Nanoparticles for Breast Cancer Therapy

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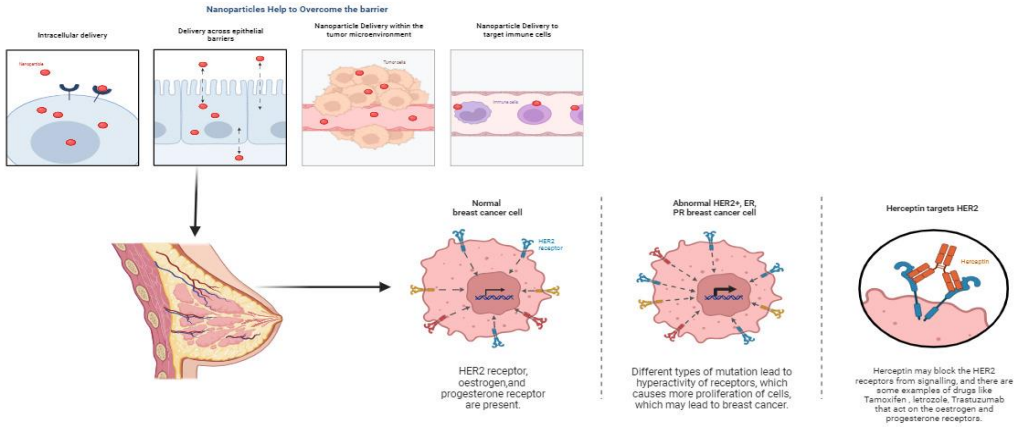
Abstract:

Cancer "Neoplasia, an abnormal mass of tissue, occurs when uncontrolled cell growth persists even after cessation of the stimulus. In the treatment of breast cancer, the use of nanotechnology makes chemotherapy more effective and harmless. The main goal of creating nanoparticles as a system for delivery is to retain the size of the molecule, exterior characteristics, and productive discharge in the absence of any undesirable effects to transport active medicine substances in the time of treatment. Drug-filled NPs are capable of breaking the blockade, and it exhibits to considerably enhance the therapeutic concentration of antineoplastic medication in brain tumours. Using NPs that are filled with antineoplastic medicine to aim cancer cells is a potential tactic that could assist in solving these problems. Utilising Nanoparticles for breast neoplasm is expanding throughout the year. Polymeric nanoparticles are often favoured nanoparticulate delivery systems in drugs, and they also comprise synthetic and natural polymers.

Keyword: Polymer, Nanoparticle, Breast Cancer



1. Introduction

Cancer is the most dangerous disease known to mankind. Improper lifestyles like unbalanced food, intake of tobacco, regular smoking, stress, and insufficient exercise influence cancer risk. Cancer has another additional risk factor that includes advancing age, and the main methods that are used for cancer therapy are surgery, radiation, chemotherapy, and immunotherapy. These methods are used globally for

the treatment of cancer. Chemotherapy and radiation therapy, despite having the capacity for cytostasis and cytotoxicity ability, are frequently connected with acute undesirable effects with increased risk of repeatability and neuropathies, subduing of bone marrow, intestinal, disorders of the skin, and alopecia as side effects [1]. Based on global cancer statistics, female breast cancer has now exceeded lung cancer as the top cause of global cancer [2]. Comparing both males and females, breast cancer is most common in females and causes cancer-related death. [3,4]. In many cases, breast cancer is commonly linked with women, despite the fact that males also have a slight probability of developing the disease [5]. The foremost treatment option for breast cancer is chemotherapy, which is supplemented with radiation therapy and surgical intervention [6]. Various mixed polymer nanoparticles have been developed to nurse breast neoplasm over the past few years. In the treatment of breast cancer, the use of nanotechnology makes chemotherapy more effective and harmless. Additional challenges breast cancer faces are metastasis and tumour recurrence [7]. Mainly breast cancer spreads through the lymphatic system; approximately 75% of lymphatic vessels clear out edgewise and eminently into axillary nodes. Treatment of breast cancer is basically based on the staging (T1 and T2) without involving the lymph node N0. It is treated by breast conservative surgery or partial mastectomy. In the early stages of breast cancer, lymph nodes may not be palpable to confirm this sentinel lymph node biopsy, but if the nodes are positive, axillary node dissection has to be done. After the surgery, additional radiotherapy is provided for locally enhanced breast cancer, and a total mastectomy is done with chemotherapy and radiotherapy. On the contrary, complete mastectomy is associated with long-term survival [8]. Nanometer size not only plays an active role in medicine but communication and interaction also affect the therapeutic result in terms of better therapies [9]. The use of nanotechnology for the preparation of anticancer medication has resulted in an industry of cancer nanotherapeutics that has experienced immense growth in the last two decades [10,11]. Polymers that are biocompatible, non- poisonous, and impurity-free are used in drug delivery systems. Other than that, they need to have a long circulation half-life and proper physical structure to fit a variety of active molecules like small molecules, oligonucleotides, and peptides [12]. Nanoparticles smoothly mingle in the human body due to their tiny size, move to desired tissues, and adhere to the target cell. Deep penetration of NPs improves the increased permeability and retaining effect. The main goal of creating nanoparticles as a system for delivery is to retain the size of the molecule, exterior properties, and productive discharge without any undesirable effects to transport of active medicine substances in the time of treatment [13]. Nanoparticles are used to enhance molecular imaging because of their unique optical and magnetic properties. Because of this, early detection of cancer is possible. Polymer nanoparticles have gained more attraction as compared to other nanostructures as they have extensive structural diversity and the ability to accomplish different composing, structures, sizes, and suitable exterior properties [14]. Chemotherapeutic agents likely cause systemic toxicity and other side effects by damaging healthy tissues while killing cancer cells [15,16]. Nanotechnology overcomes various obstacles standing in the line of an effective and safe drug delivery system [17,18]. Therapeutic agents of interests are encapsulated within the NPs, which are submicron-sized polymeric colloidal particles, and they are adsorbed or conjugated to their surface [19,20]. Protecting them from being quickly metabolised and excreted by the reticuloendothelial system, kidney, and liver, the polymeric nanoparticle system can enhance the stability and specificity of the loaded drug [21,22].

Breast Cancer Classification

Breast is a modified sweat gland that consists of ducts, lobules, and stromal tissue. uncontrolled proliferation of any component gives rise to new tissue that has the capacity to grow in the absence of growth in absence of growth stimulus, neovascularization, metastasis and invasion.

Risk factors: not only genetic but also environmental factors contribute to cancer.
Examples: genetic factors: brca1, brca2, p53, chek2.

On the basis of histopathology, breast cancer classification

- Non-invasive
- Invasive

Non-invasive has two types

- Ductal carcinoma in situ Involves the terminal duct lobular unit, in which the malignant cell proliferates in the duct without breaching the membrane.
- Lobular carcinoma in situ clinically, no mass is palpable; only incidentally diagnosed on biopsy, which shows discohesive tumour cells due to a lack of the E- cadherin gene.

Invasive tumours

Most common type of breast cancer. It can be clinically and radiologically detected when its size is >2cm and >1cm, respectively.
On histopathology, the cells are arranged as irregular cords, nests, and breaches in the basement membrane.

On the basis of cellular arrangement, they are classified as

- Tubular cancer which is well differentiated and has the best prognosis ER PR is positive and HER 2 is negative.
- Medullary cancer tumour cells arranged as solid syncytium-like sheets with pleomorphic nuclei and surrounded by lymphocytic infiltrates
- Mucinous cancer in this tumour cells floats in mucin

Various Stage of Breast Cancer

stage Ⅰ **A** Primary tumour less than or equal to 20mm size with no lymph node involvement and no metastases present.
Stage Ⅰ B primary tumour of size less than 20mm with nodal micrometastases of size greater than 0.2mm and less than 2mm and no metastases present.
Stage Ⅱ A primary tumour of size equal or less than 20mm there is the involvement of the N1 node and if size is less than 20mm or less than 50mm no nodal involvement.
Stage Ⅱ B primary tumour of size greater than 20mm and less or equal to 50mm there is involvement of N1node while in size greater than 50mm no nodal involvement and no metastases present.
Stage Ⅲ A primary tumour of size equal or less than 50mm there is involvement of N2 nodes while size greater than 50mm has N1or N2 nodes.
Stage Ⅲ B primary tumour irrespective of size infiltrates into the skin example ulceration, peaudorange and nodes from N0 to N2.
Stage Ⅲ C Any size of primary tumour with N3 node
Stage Ⅳ C primary tumour with metastases of any size and any nodal involvement is classified as stage Ⅳc.

Figures

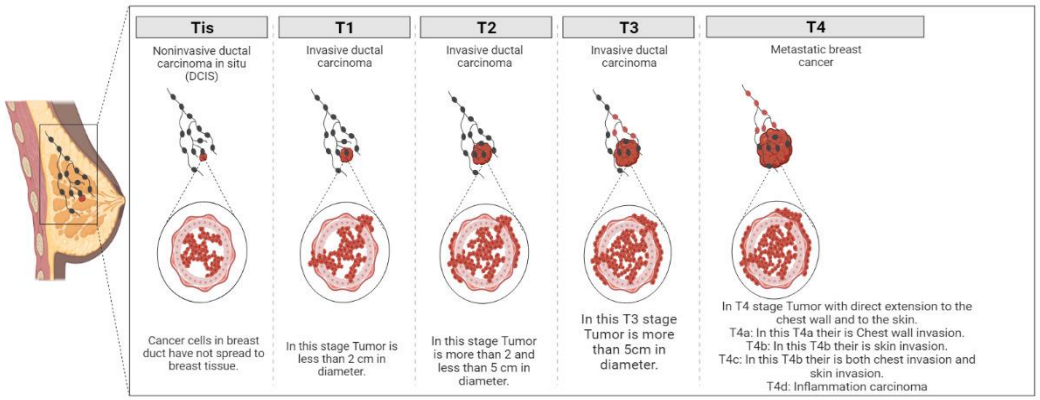


Figure 1: It represents the stages of breast cancer

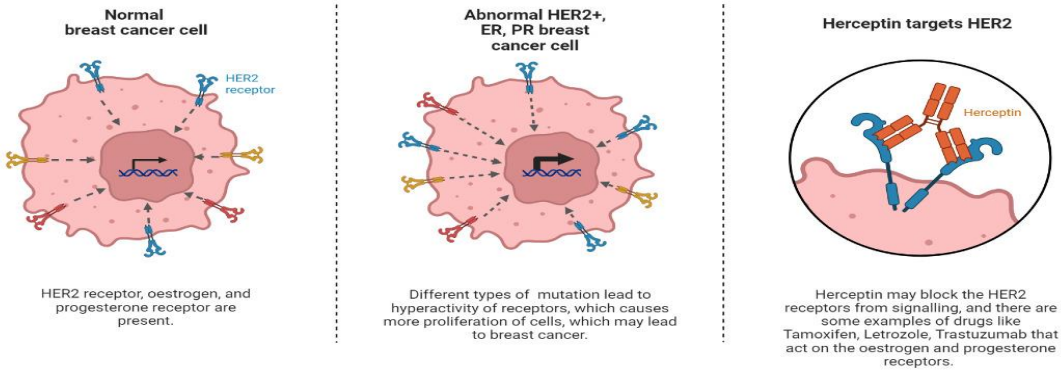


Figure 2: Mechanism of drugs targeting the hormonal receptor

Nanoparticles for Treatment of Cancer as a Drug Delivery System:

The ability of the nanoparticles as putative medicine delivery system is recognised as these provide variety of benefits as comparison to the convention therapy. For formulation of NPs polymers utilised should be biocompatible and biodegradable [23,24]. Release of drug from Nanoparticles be able to restrained by adjusting polymer properties to attain a desirable therapeutic stage in target tissue for necessary time for best therapeutic efficiency and discharge of a continuous quantity of medicine per unit time. Drug-filled nanoparticles are capable of breaking this blockade and exhibit to considerably enhance therapeutic concentrations of antineoplastic medication in cerebrum tumour [25,26]. Another vital issue that assists to the opposition of tumours to antineoplastic medicines is multidrug resistance connected to p-glycoprotein. Using NPs that are filled with antineoplastic drug to aim cancer cells is a potential tactic that could assist to solves these problems. Drug targeting can be attained by actively aiming drug transporter utilising target particular ligands or passively targeting drug transporter by making use of unique pathophysiological characteristics of tumour tissue.

Mechanism of Action of Polymeric Nanoparticles

Burst discharge, dispersion through polymer matrix, and erosion are the three methods that regulate the discharge of medicated content from polymeric nanoparticles.The discharge of medication from polymeric NPs is anticipated to be a triphasic profile [27].

Stage Ⅰ: This phase is regulated by the burst method. The medicines are delivered through the desorption-diffusion process and they are physically adsorbed across the surface of the NPs. This phase is distinguished by limited times.

Stage Ⅱ: The release phenomena explained by the therapeutic diffusion via pores and matrix. This stage can coincide with polymer erosion and is significantly slower [27,28]. The diffusion depends on the interaction between molecules therapeutic or polymer effect, and additionally on the permeability and thickness of the nanodevice [29]. Discharge of aqueous dissolvable and less-solvable medicine inserted in the semisolid and solid matrix and described by Higuchi pattern a mathematical representation this procedure is followed by stage 1 and stage 2. Thus, the uncomplicated Higuchi model is established on the pseudo-steady situation that proceeds towards and fits the fick's first rule for a perfect steady-state phase Ⅱ that explains the discharge of medicines as a square root of a duration-independent mechanism [27].

StageⅢ: This case is based on the physical and chemical characteristics of the unprocessed products, and the erosion method will guide this stage [27]. Mainly the discharge process is very limited. Some polymers are effortlessly hydrolyzed and exhibit this stage in quick periods. The discharge kinetic is uncertain in this stage [30]. To involve both fickian and non-fickian discharge of medicine from the polymeric matrix, both Korsmeyer and Peppas models depend on a mathematical model. This explains the discharge as a duration-dependent t n mechanism, in which n represents exponent discharge and indicates method of drug transfer across polymeric matrices, and this allows erosion mechanism that will incorporate into the discharge process in stageⅢ [31]. Both the biphasic and continuous discharge characteristics have been explained.

Breast Cancer: Detection, Molecular Targets

Oestrogen receptor alpha (Erα) and epidermal growth factor-2(ERBB-2) are the major molecular targets that are participating in pathophysiology of breast neoplasm. Mainly in 70% case of invasive breast cancer illustrate the steroidal hormone receptor Erα. In 20% of breast cancers Basal-like-1 TNBC ERBB-2 is over -expressed and distinguished by increase respond to DNA harm along with Ki67 level. The androgen receptor is highly demonstrated in the luminal androgen receptor and tenfold greater than another subtype. The mesenchymal stem -like TNBC differentiated by means of components which will connect with G-protein receptor, Ca signalling, and EGFR. Enhanced manifestation of STAT genes which regulate T and B-cells and natural killer cells, thought to be source of immunomodulatory TNBC [32].

Existing Breast Cancer Treatment Limitations

Present therapy tactics have various drawbacks in the cure of breast neoplasm, that involves shortage of particular toxicity, and that results in reduced therapeutic efficiency as a result impaired medicinal indicative; damage to health tissues, a reduced dosage of anti-cancer drug that is normally administered to lower the toxicity to healthy tissues; inadequate bio-distribution and medicine incorporation in solid tumours; heterogenic vessels in the site of tumour raises extravasation of drug [33]. Present therapy tends to higher medicine disposition in normal viscera (ten to twenty times stronger) as compared to the comparably filled tumour site, and various chemotherapeutic agents are not able to penetrate from the vasculature beyond 40-50mm which leads to multiple drug resistance and ultimately therapeutic failure [34,35].

Nanoparticles for Drug Delivery: Types

Carbon nanotubes, dendrimers, extracellular vesicles, liposomes, tunneling nanotubes, and polymeric nanoparticles are different types of nanoparticles used as drug conjugates [36].

Liposomes

Bi-layered vesicles are known as liposomes and are comprised of the external lipid bilayer that surrounds the internal water core [37,38]. They have restricted medical impact due to their stability-related matter however significantly utilise cosmetic components. Besides performing function utilising polyethylene glycol enables for longer circulation periods. Doxil, Myocet, and Daunoxome are liposomal formulations that are accepted for metastatic breast cancer.

Carbon Nanotubes

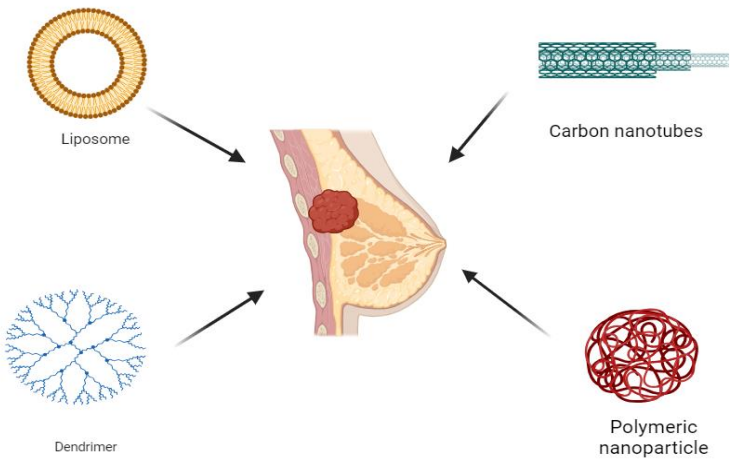
Moreover, chemical alteration of carbon nanotubes makes them dissolve also operationalize in such a way that active constituents such as medicines and peptides can bind to the exterior [39]. The use of nanoparticles causes acute toxicity, carcinogenesis, and immunogenicity that cannot be ignored. Thus, they needed to be chemical or biological altered prior utilisation for cellular delivery. Characteristics such as less biocompatibility limits its utilisation.

Dendrimers

They are in micromillimeter scale with several subdivide monomers emit out from the medial core and it is a synthetic polymer-establish large molecule. supposing the gap at the medial, polyvalence, simplicity of exterior alteration, precise globose, anticipated weight of molecule, absence of immunogenicity, aqueous solvable and restraint of size make them a useful choice for delivery [40].

Polymeric Nanoparticles

They are comprised of polymers and copolymers that protect a medicine, as well as encapsulated inside particle or consumed across the exterior or chemically attached to the exterior, easily and these have size range of 10 to 1000nm [41,42]. They stated it contains a central-shell design with inner comprising of a polymeric matrix having lipophilic and the exterior is made up of lipophobic polymers [43]. Polymeric nanoparticles end products are harmless alcohols with less weight of molecule compounds, polymeric nanoparticles are biodegradable. Conventional treatments have various complications that can be reduced when utilising polymeric nanoparticles.



Developing Technology For Breast Cancer Treatment :Polymeric Nanoparticles

Key Properties Of Polymeric Biomaterials

To produce polymeric nanoparticles to obtain rapid and effective clinical translation biocompatible polymers must be used. poly-lactic-co-glycolic acid (PLGA), poly-lactic acid (PLA), polyethylene glycol (PEG), chitosan, alginate, and pectin are the examples of polymers utilise for the production of polymeric nanoparticles[44,45].

Active Targeting

Molecular identification of cancer cells through ligand-receptor, interaction of Ab-Ag or through aptamers there is targeting, active targeting to the tumour can be attained. Targeting agents that attached across the exterior of nanocarriers involves protein, that is antibodies, peptide, aptamer, nucleic acid, vitamins, and carbohydrates [46,47]. Targeting agent must be adequate, have increased affinity and particularity of bonding to cell exterior receptors and appropriate to chemical alteration by conjugation in order for drug targeting to be successful.

Passive Targeting

To deliver drugs at the therapeutic site passive targeting utilises the anatomic dissimilarity within healthy and tumour tissues. Increased permeability and retaining effect permit extravasation of circularise polymeric nanoparticles through the tumour interstitium and higher concentration of chemotherapeutic agent inside tumour tissue [48,49]. Enhanced permeation and retention effect (EPR) could be used passively guide circulating nanoparticles into tumour cells. Solid tumour develops to specific size and the normal vasculature is not sufficient to provide the oxygen needed for multiplication. When tumour cell starts to degrade, they release growth factor which enhances angiogenesis that is growing of new blood vessels from nearby capillaries increases the permeability of the surrounding tissue. Fenestration capillaries range from 200 to 2000nm which facilitates extravasation of nanocarriers from nearby vessels into cancerous cells.

Polymeric Nanoparticles Are Currently Researched As A Treatment For Breast Cancer

Table 1: Drugs and Polymers used in Breast cancer treatment

Classification	Drug	Mechanism of action	Polymer
anthracycline	Doxorubicin	Inhibit topoisomerase-2 in S-phase	Poloxamer 407, holo-transferrin
EGF(HER) receptor inhibitor	Erlotinib	Inhibit epidermal growth factor	N,N-diisopropylethylamine, N-hydroxysuccinimde
Selective estrogen receptor modulator	Tamoxifen	It has effective partial agonist action in utero while it has effective oestrogen antagonistic action in breast cancer cell	Pluronic F-68, Pluronic F-108, Poly-(ethylene oxide)-modified polycaprolactone

Taxanes (M-phase inhibitor)	Paclitaxel	It promotes mechanism of action, promote polymerization of tubulin molecules as a result this stack and fall to polymerize and get arrested, frozen in meta phase.	Polyethoxylated castor oil (Cremophor)
Taxanes	Docetaxel	Stimulates beta tubulin and increases polymerization of microtubules, prevents depolymerization	Triethylamine, PLGA, antibody conjugated magnetic nanoparticles
Alkaloids and derivative	Piperine	It inhibits human P-glycoprotein and cytochrome P4503A4	PLGA
Immunomodulator	Rapamycin	m-tor inhibitor	PLGA
BCR-ABL tyrosine kinase inhibitor	Dasatinib	It binds to both active and inactive states of the enzyme.it is also a more potent inhibitor.	Poly (cyclohexene phthalate)
Organic compounds(curcuminoids)	Curcumin	inhibiting proliferation and invasion of tumors.	Bovine serum albumin
Antibiotics	Doxorubicin	These interpolate within DNA strand and blocking DNA along with RNA production. Their more prominate action is to combine with and activate topoisomerase-2 causing breaks in DNA	PLGA 50:50
K^+ ionophore antibiotic	Salinomycin	It inhibits HIF-1α transcription factor activity	PLGA
Vitamin D	Calcitriol	Increase the production of	PLA

		calcium transport proteins, which leads to increase uptake of calcium	
Folate antagonists	Methotrexate	It inhibits dihydrofolate reductase and blocks the dihydrofolic acid to convert into tetrahydrofolic acid	PLGA, resomer
Taxane	taxols	Stimulates tubulin and increases polymerization of microtubules, prevents depolymerization.	PLGA
flavonoid	Baicalin	Suppression of inflammatory markers, COX-2, TNF-α, and IL-6 expression	Tween 80, labrafil M2125 CS oil, poloxamer P407, PLGA
Vinca alkaloids	Vincristine	It inhibits microtubule formation and synthesis of DNA or RNA. It arrests the cell in metaphase by disrupting the formation of the mitotic spindle. It binds to protein of mitotic spindle causing metaphase arrest.	PLGA, PEG, folic acid (conjugation)
HMG-CoA reductase inhibitors (statins)	Simvastatin	It acts by antagonistically inhibiting the HMG-C0A conversion to mevalonate with the help of enzyme HMG CoA reductase.	Cholic acid, PLGA
Platinum coordination complex	Cisplatin	The platinum coordination complexes reach	Poly(2-oxazoline)

		cells next they perform intracellular hydrolysis to generate a highly reactive moiety that leads to DNA crosslinking.	
Monoclonal antibodies (HER) receptor inhibitor	trastuzumab	it binds to extracellular domain of another subtype of EGFR termed HER2 and inhibits signal transduction	Chitosan, D-α-tocopherol polyethylene glycol 1000 succinate
Aromatase inhibitors	Letrozole	It reversibly inhibit aromatization in fact that in breast cancer cells, results in directly complete oestrogen shortage in post-menopausal female.	Poly (D, L-Lactide)
Aromatase inhibitors	Anastrozole	It reversibly inhibits aromatization and utilize as adjunct treatment in earlier ER^+ breast carcinoma and additionally for advance case soothing in postmenopausal female.	Polycaprolactone, PEG, stearic acid
Vinca alkaloids	vinorelbine	Mitotic inhibitor which binds to microtubular protein-tubulin, prevents its polymerization and assembly of microtubules, causing disturbances of mitotic spindle and hinder with cytoskeletal functions.	PLGA, PEG, aptamer

EGF receptor inhibitor	Lapatinib	This is orally active inhibitors of EGFR/HER2 which penetrates cells and block tyrosine kinase activity of the liganded HER2 and interferences with signal transduction	Tocopheryl polyethylene glycol-1000 succinate, PLGA

Table 2: Recent patent on the use of nanoparticles in breast cancer therapy

Patent name	inventor	Year
Compositions and methods for use in oncology	Laurence poul, Laurent Levy, Celine Berjaud, Matthieu Germain, Agnes Pottier	2021
Targeted nanoparticles for cancer diagnosis and treatment	Jie Chen, Wilson Roa	2017
Nanoparticles for use in cancer therapy	Howard R Petty	2019
Combination chemotherapy regimens using albumin/paclitaxel nanoparticles and nucleoside analogs	Neil P. Desai, Patrick Soon-Shiong	2019
HER2-targeted phase-change PLGA nanoparticles, application and preparation method.	Deng, L.; Sun, Y.; Wang, Z.; Liu, M	2019

2. Conclusion

Present therapy tends to higher medicine disposition in normal viscera (ten to twenty times stronger) as compared to the comparably loaded tumour site, and various chemotherapeutic agent not able to penetrate from the vasculature above 40 to 50mm which leads to multiple drug resistance and ultimately therapeutic failure. Due to increase in drug -therapeutic efficiency nanoparticles provide various benefits in medicine. Polymeric nanoparticles are often favoured nanoparticulate delivery system in drugs, and they also comprise natural polymers and synthetic polymers. Utilising Nanoparticles for breast cancer expanding over time and polymeric nanoparticles present a buoyed-up discharge of encapsulated drug, assist to prevent the drug from the body's enzymatic, acidic, deterioration state, give the ability to target from a propensity for a passive accumulate in tumours, and show adjunct properties. Due to these characteristics form this kind of nanoparticle a satisfactory technique to avert cancer attack.

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Conflict of interest

The authors declare that there is no conflict of interest.

Abbreviations

NPs- nanoparticles; **DNA-** deoxyribonucleic acid; **STAT-** signal transducer and activator of transcription; **TNBC-** triple negative breast cancer; **EGFR-** epidermal growth factor receptor; **Ab-Ag-** antigen- antibody

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