



## **Advances in Nanomaterials-Based Carrier System for the Treatment of Breast Cancer**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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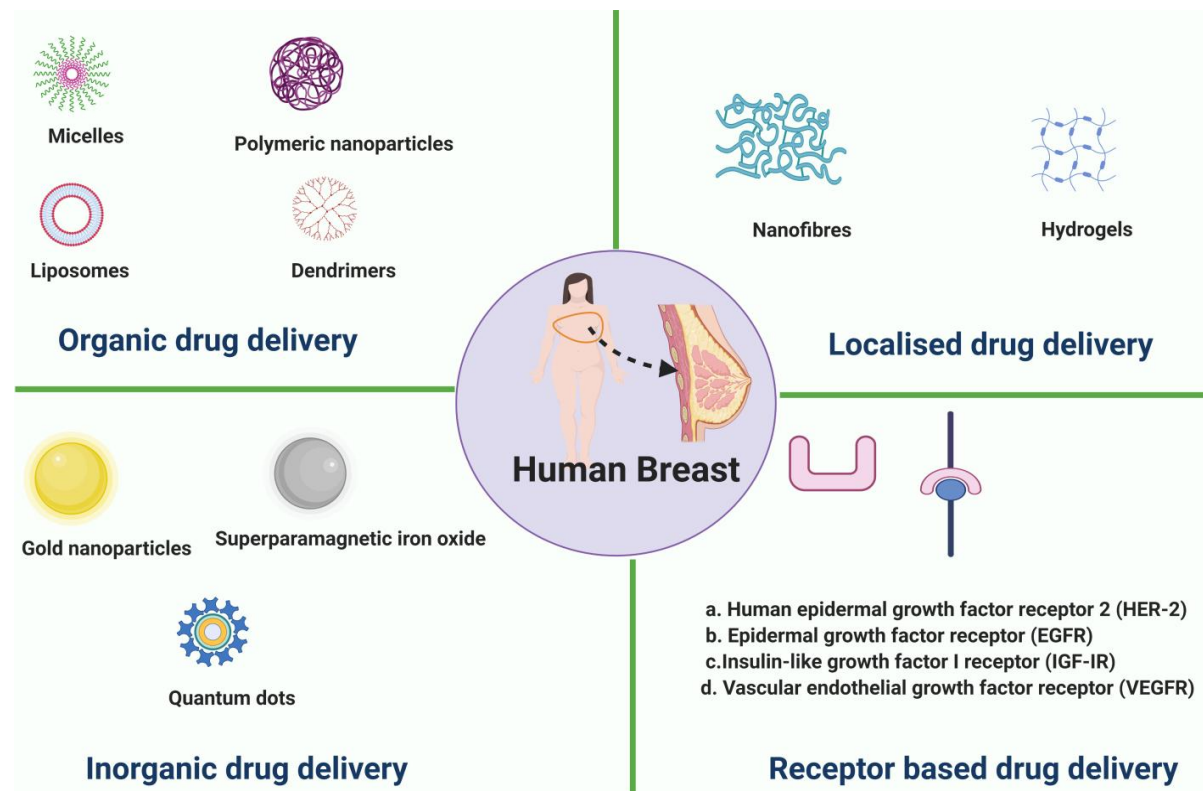
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### **ABSTRACT**

Nanotherapeutics for the cure of breast cancer remains unswervingly succeeding and being practiced to eradicate innumerable restrictions of conventional practice obtainable for the supervision of breast cancer. Nanoparticles offer an interdisciplinary extent for exploration in imaging, diagnosis and targeting of breast cancer. Through a progressive physicochemical features and improved bioavailability, they spectacle persistent blood circulation through effective tumor targeting. Nanoparticles remain capable to diminish cytotoxic consequence of the active anticancer medications through amassed cancer cell targeting in contrast to conventional preparations. Several nanoparticles-based preparations remain in the preclinical and clinical phases of progress; amongst them, polymeric drug micelles, liposomes, and dendrimer, remain the utmost common. In this review, we have conferred the role of nanoparticles through detail to oncology, by predominantly aiming on the breast cancer and several nanodelivery systems practiced for targeting action and signaling forces through further intracellular pathways in breast cancer.

**Keywords:** Breast cancer; nanoparticles; nanoengineered, Anti-Breast cancer drugs; nano-drug delivery system.

## GRAPHICAL ABSTRACT



## 1. INTRODUCTION

Breast cancer (BC) remains one of the utmost prevailing malignant disorder in women globally. BC is a heterogeneous ailment at the molecular level and remains confirmed to be the second foremost source of human cancer-related demises [1]. Generally, it affects one in 20 women and one in eight in high-income countries [2]. 2.1 million individuals remain spotted through breast cancer every year [3]. The five years relative survival of localized BC after diagnosis in the United States (US) is 98.8%, 85.5% for regional cancer, 27.4% for distant cancer; 54.5% for unknown disease conditions [4]. It remains a significant source of cancer illness and death. An approximate 627,000 women diagnosed with breast cancer in 2018 [5]. In comparison, just 1 percent of all malignant breast neoplasms account for BC in males [6]. Paralleled to women, men appear to remain spotted with BC by age 67 [7]. The highest BC prevalence has been recorded in Belgium, with 111.9 per 100,000 age standardized. Denmark recorded the second highest outbreak of BC, through an

age-standardized level of 105 per 100,000 people. Statistics indicate such North America and Oceania were the utmost recorded occurrence of BC, while Asian and African were the lowest [8-9].

While being the utmost prevailing form of cancer in women, it is deemed treatable if detected at early stage [10]. BC is a disease of the glandular breast tissue that is most generally discovered as an asymptomatic nodule on a mammogram before any signs appear [11]. Tumor blocks lymph channels in inflammatory breast cancer (IBC), which can cause discomfort, swelling, heat and redness around the breast and orange skin texture [12]. Benign breast cancer involves all non-malignant breast disorders, including benign cancers, injuries, mastalgia, mastitis, and nipple discharge [13]. Many of BCs normally starts in the lobules and in the ducts that bind those lobules towards the nipple. Uncontrollably accelerated progress of all these cells has contributed unswervingly towards the production of cancer cells, which are generally seen as lumps that can be seen on x-rays. As the mass of the tumour

increases, it progresses in the form of malignant cells, whether they infiltrate or metastasize to some parts of the body and circulate more in the surrounding cells [14]. If metastasis is accomplished, however it can spread at very fast rate to distant organ via the blood and lymph systems, raise treatment difficulties and increase mortality rates. Metastatic signs of breast cancer may involve bone, lung, pulmonary and brain invasion. Unexplained weight loss may cause occult breast cancer, fever, or chills. Pleural effusion is typical to metastatic breast cancer [15]. The prevalence of invasive breast cancer remains highly determined by the disease level, i.e. the degree or distribution of cancer when first diagnosed. Each breast cancer has four stages of cancer seriousness, as revealed in Fig. 1.

Women by high threat of BC have a range of ways towards ease their menace, comprising medications and regime choices. The management of BC remains multi-disciplinary; the option of cancer care depends on many variables, including level, position and size of the tumour, histology and tumour unique characteristics, but also on the age and pregnancy of the patient [16]. The main purpose of these treatments is to remove cancers thereby prolonging the life of patients, while many therapies are possible, spanning from surgery to chemotherapy, most of these treatments are

questioned in terms of tumour recurrence and drug resistance. As reported, chemotherapy has significant side effects owing to its lack of precision [17]. Cytotoxic impact on naturally proliferating cells and accumulation of therapeutic tolerance from cancer cells are typical causes for inefficiency of chemotherapy and eventually contribute to death [18]. Since the development of innovative medicines is very time-consuming and expensive, it is important to look at potential alternatives [19]. Alternatives may be to repurpose medicines or produce drugs based on the combination of previously developed drugs and other molecules to enhance bioavailability, specificity and stabilisation of the active component often known for instance the drug delivery system (DDS) growth. In concern of these side effects of classic cancer therapy methods, new beneficial alternatives must be found.

Alternatively, the usage of nanomaterials has recently developed particular attention for instance an important drug distribution tool for the management of cancers. Continuing investigations required to refine this strategy to potentially reduce the detrimental consequences of traditional methods. The integration of new delivery mechanisms will contribute to a successful method for early detection, successful care and proficient management. Presently,

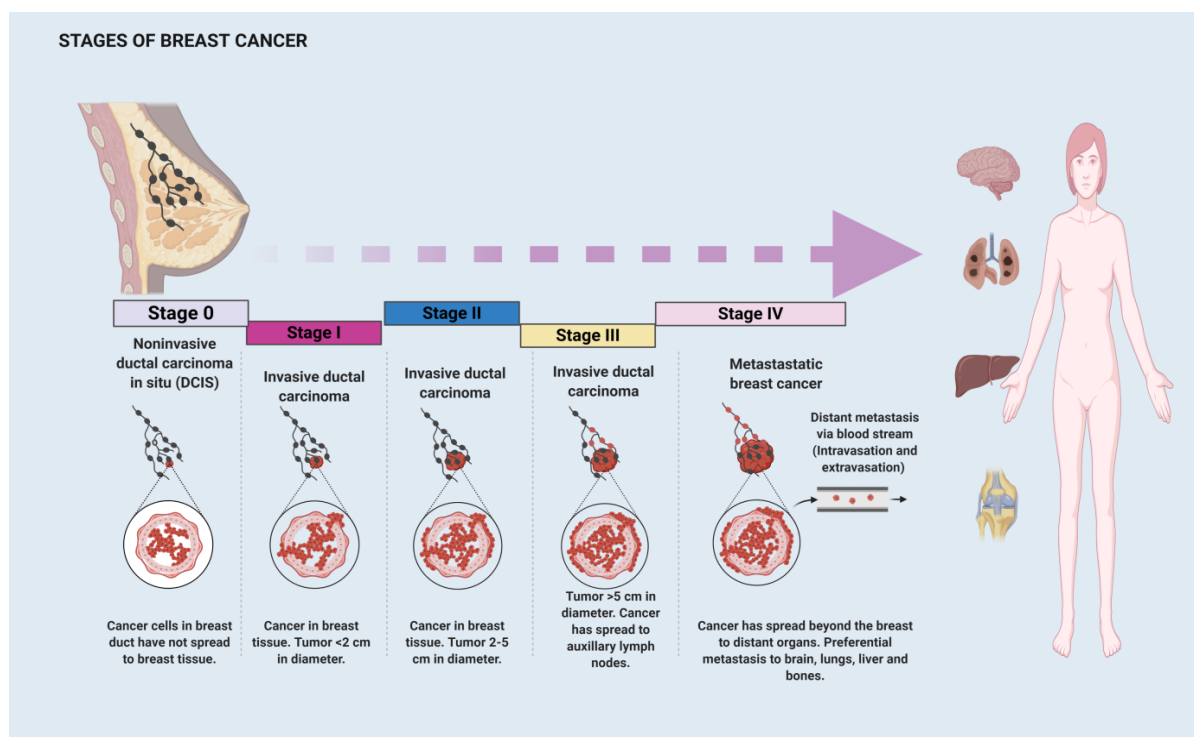


Fig. 1. Different stages of occurrence of breast cancer

cancer exploration is centred on developing BC therapy utilizing numerous innovative chemotherapeutic agent delivery mechanisms, aforesaid nanopreparations, liposome, hydrogel, exosome, dendrimer, microsphere, microbubble, phytosome, micelle, etc. Table 1 summarizes the major nanocarrier expressions developed for the treatment of breast cancers.

**Table 1. Approaches of nanotechnology centered DDS and employed for breast cancer therapy**

Drug	Application	Reference
<b>Dendrimer Drug Delivery System</b>		
Curcumin	To get enhanced solubility and cytotoxicity	[24-25]
Docetaxel	To boost the efficiency of cancer cell killing by reducing the tumour cell's volume and weight.	[21-23]
Doxorubicin	Eradicate drug-toxicity and surges drug effectiveness	[27,28]
5-Fluorouracil	Synergistically persuade apoptosis	[20]
Trastuzumab	A humanized monoclonal antibody and recombinant for instance a target remedy	[26, 29-30]
<b>Exosomes Drug Delivery System</b>		
Adiramycin	Provide increased drug resistance by using miR-222 as a transport mechanism.	[34]
Docetaxel	Controlling cell death by intercellular transfer of particular miRNA	[34]
<b>Hydrogels Drug Delivery System</b>		
Cisplatin	Antitumor activity towards MCF-7 BC cells and human colorectal cancer cells was improved.	[30]
Docetaxel	Enhance oral bioavailability	[29]
Taxol	Acquire targeted distribution and greater in vitro antitumor efficiency	[28]
<b>Liposomes Drug Delivery System</b>		
Anastrozole	At post-menopausal phase of women advanced breast cancer should be treated.	[35]
Gemcitabine	Enhance cytotoxicity	[43]
Epirubicin and Quinacrine	Show significant antitumor effectiveness across the board and prevent VM channel degeneration following chemotherapy	[36-37]
Doxorubicin	Increase the efficacy of medication delivery to EGFR2 overexpressing cells.	[38]
Mitoxantrone	Increase anti-cancer effectiveness while lowering medication toxicity by targeting the plasma membrane.	[41]
Oxaliplatin	To enhance MT-3 breast cancer treatment and metastases in a mouse xenograft	[42]
Paclitaxel	To improve chemotherapeutic efficiency	[40]
Rapamycin	Produce cytotoxicity in human EGFR 2-positive breast cancer cells	[39]
Salinomycin& Doxorubicin	Target cancer stem cells	[45]
Sinitinab and Vinorelbine	Achieve a more precise delivery	[44]
<b>Micelles Drug Delivery System</b>		
Curcumin	To achieve a synergistic impact	[33]
Doxorubicin	Multidrug resistance is reversed	[31]
Paclitaxel	Get higher toxicity in comparison with taxol	[32]
<b>Nanoparticles Drug Delivery System</b>		
Curcumin	Elevated solubility of the drug	[47]
Damnacanthal	More effective cell growth inhibition	[50]
Docetaxel	Carry higher levels of drug than linear polymer	[49]
Doxorubicin	In order to be successful in suppressing proliferation and induce apoptosis	[46]
Lapatinib	Reduce the dose regimen in order to obtain the best therapeutic result	[48]
Paclitaxel	Deliver drug/siRNA targeting/gene	[51]
Simvastatin	Acquire a much higher cytotoxicity level	[52]

Since, breast cancer is a global issue, the worldwide inequalities in access to multi-modal care and emerging medication carriers must be illustrated. In current review, we address the process of selective drug distribution nanoparticles and the recent development in therapeutic strategies through nanoparticle-based carriers. We are also exploring the potential opportunities and difficulties of nanoparticle-based breast cancer treatment. Clinical translation of useful technologies focused on nanotechnology is underway rapidly and has significantly revolutionised the in the area of cancer treatment. Some of the approved and clinical trials therapies are listed in the Table 2.

## 2. NANOCARRIER SYSTEM FOR TARGETED DRUG DELIVERY IN BREAST CANCER

Nanotechnology remains a discipline involving the modification of matter on an atomic, molecular and supramolecular scale of some to several hundred nanometres. For the past two decades, nanotechnology playing significant role in the development of drug delivery mechanisms, addressing the shortcomings of traditional carriers. Using nanoparticles is an evolving platform used for cancer care [53].

**Table 2. Nanotechnology related approved drug therapies for breast cancer**

Product	Manufacturer	Nanotechnology Employed	Status
Abraxane®	Abraxis Bioscience	Albumin assured paclitaxel nanoparticle	Permitted in 2005
BIND-014	BIND	PEG-Poly(lactic-co-glycolic acid)/docetaxel	Phase II
Caelyx®	Orthobiotech, Schering-Plough	PEGylated liposomal/doxorubicin hydrochloride	Approved in 1995
Doxil®	Janssen Products	PEGylated liposomal/doxorubicin hydrochloride	Approved in 1995
EndoTAG-1	Medigene/SynCore Biotechnology	Paclitaxel embed in liposomal membranes	Phase III
Genexol®-PM	Samyang Biopharmaceuticals	Polymeric micelle PEGpoly(D,L-lactide) loaded with paclitaxel	Phase III
Lipoplatin®	Regulon	Liposomal Cisplatin	Phase III
Liposomal annamycin	New York University, School of Medicine	Liposome/ semi-synthetic doxorubicin analogue annamycin	Phase I/II
Liposomal Captured Paclitaxel-Easy To Use (LEP-ETU)	INSYS therapeutics, Neopharma	Liposomal Paclitaxel	Phase II
Myocet®	Elan Pharmaceuticals, Sopherion Therapeutics	Non-PEGylated liposome of doxorubicin	Approved in 2000
Narekt-102	Nektar Therapeutics	PEGylated liposome loaded by Irinotecan	Phase III
Nanoxel®	Fresenius Kabi Oncology	PEG-poly(D,L-lactide)/docetaxel	Phase I
NK-012	Nippon Kayaku	PEG-Polyglutamic acid/ SN-38	Phase II
NK-105	Nippon Kayaku	PEG-polyaspartate/paclitaxel	Phase III
Rexin-G	Epeius Biotechnologies Corp.	Targeting protein tagged phospholipid/ micro RNA-122	Phase II/III
S-CKD602	Alza	PEGylated liposomal/CKD602	Phase I
SPI-077	LiPlasome Pharma	Stealth liposomal cisplatin	Phase I/II
ThermoDox®	Celsion	Heat-activated Liposomal Doxorubicin	Phase I/II
Xyotax®	Dana-Farber Cancer Institute	Paclitaxel Poliglumex	Phase II

The National Nanotechnology Initiative (NNI) describes nanotechnology with measurements of approximately 1 to 100 nanometers (nm) in terms of scale restrictions [54]. Particles within this class tend to be suitable for many critical functions as nano-carriers, comprising modifying the drug's interaction, potency, electrical features, and eventually *in vivo* behaviour. Ideally, nano delivery systems would allow for more accurate targeting of the medication, while enhancing effectiveness and minimising side effects. Through expending nanotechnology in drug design and controlled distribution, researchers remain attempting to drive nanomedicine transmit towards the target tissue, release the medication at a precise rate, and offer a biodegradable DDS. The different type of nanocarriers, which are widely preferred for breast cancer treatment is shown in Fig. 2.

Nanoparticulate DDS provide diverse benefits for cancer treatment above permitted drug management due to following reasons: 1)boost

the healing index of loaded chemotherapeutic means relative to traditional treatment medicines; 2)enhanced bioavailability by the enhancement of aqueous solubility; 3)increased extent of stay in the body; 4)the targeting of the drug at a precise position in the body which consequences in a concomitant decline in the necessary medication quality and dose toxicity, permitting the benign distribution of toxic healing medications and the fortification of non-target tissues and cells from serious side effects [55].

## 2.1 Organic Drug Delivery Approaches

Organic NPs have been extensively studied for various kinds of materials for decades.Organic nanocarriers are biocompatible in nature with large drug encapsulation and loading. Medications can remain substantially captured or chemically conjugated within organic nanocarriers [56].

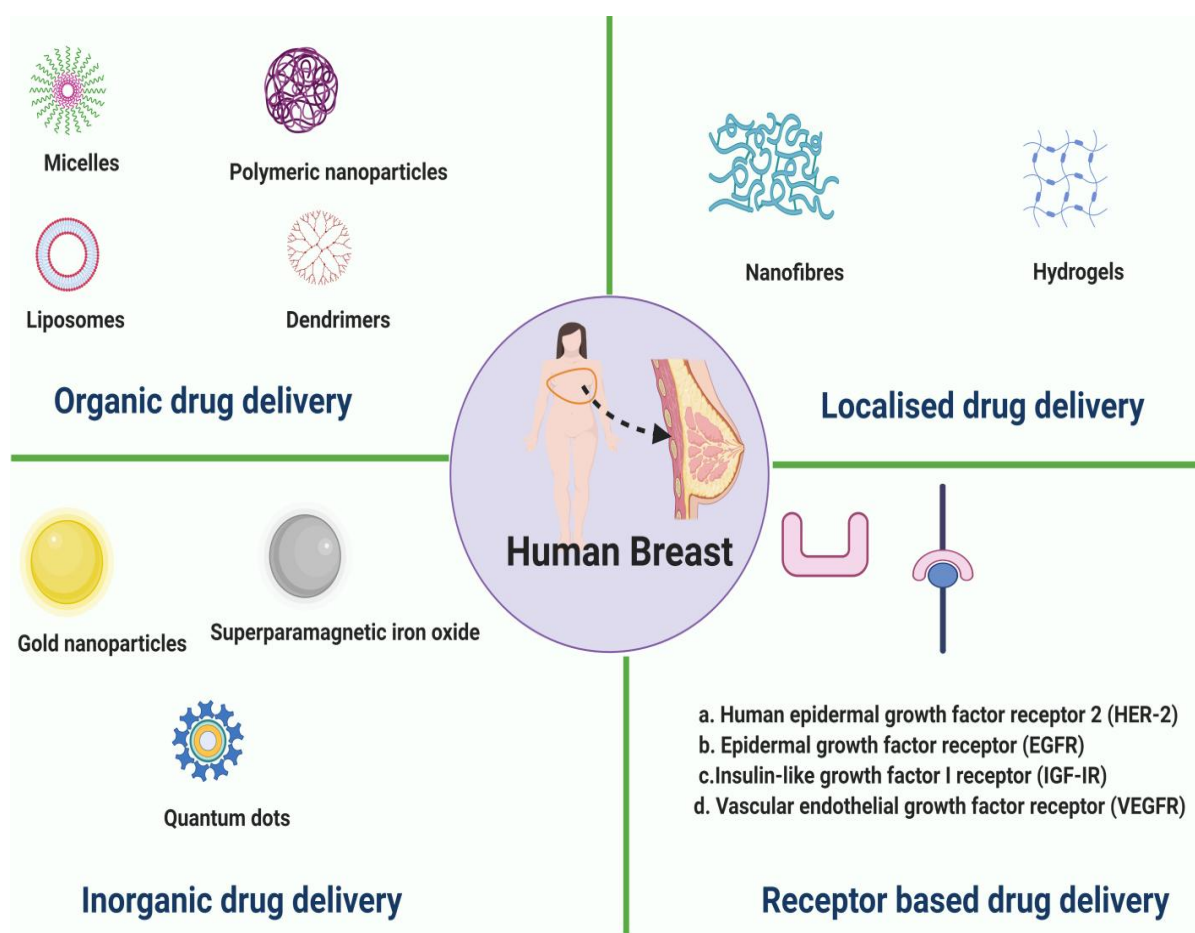


Fig. 2. Common nanomaterials for treatment of breast cancer

### 2.1.1 Micelles

Polymeric micelles (PMs) remain colloidal elements designed after conjugations of polymers which are water soluble of phospholipid or extensive chain fatty acids and added surfactant. PMs remain mostly characterised as amphiphilic copolymers by polymer self-assemblies in nano-assemblies constitute another commonly researched form of polymer NPs [57]. Breakthroughs in the mixture of biocompatible and biodegradable amphiphilic block polymer through constricted molecular weight distribution and well-distinct polymer block obligate allowed the preparation of polymer micellar nanocarriers through extents array from 10 to 200 nm via self-assembly processes. The hydrophobic block shape at the centre of the micelle and the shell of hydrophilic polymers stabilises the micelles in an aqueous solution and keeps the payload phase [58]. The hydrophobic core helps insoluble anticancer drugs for uniform absorption and smooth distribution. While the hydrophilic portion improves stability, reducing reticuloendothelial absorption of the medication and prolonging its circulation period [59]. Micelles build up in poorly vascularized tumours and boost the permeability and retention of anticancer agents, and increase half-life [60].

Wang et al., reported advanced composite oral DDS for the treatment of BC. It was based on docetaxel-charged micelle in pH-responsive hydrogel (DTX-micelle-hydrogel). Docetaxel remained effectively loaded in micelle through size range of element 20 nm with 7.76 % drug load. Cytotoxicity studies with 4T1 cells have shown the successful antitumor behaviour of DTX micelles [29]. Doxorubicin for the treatment of metastatic BC by redox-responsive hyaluronic acid-ibuprofen prodrug micelle was reported by Chai et al, [61]. The doxorubicin-loading micelles of HA-ibuprofen prodrug (HA-ss-BF) inhibited *in vivo* primary tumour development and breast cancer metastasis. Redox-sensitive polymeric micelles have several clinical benefits and might remain a probable delivery mechanism for metastatic BC treatment. Kwa and co-workers investigated the incorporation of Static into the amphiphilic pendant-dendron copolymeric (P71D3) mice to enhance its distribution within tumour cells and water-solubility. The optimized ratio of P71D3/Static micelles was 1:1.2 with particle size 164 nm and drug loading of 52% w/w. In acidic tumour environments, these P71D3/Static micelle recorded greater drug

release (32%) relative to neutral physiological conditions (14%). In murine mammary cancer cells and metastatic human BC, P71D3/Static micelles were found 30- to 90-folds more potent. There is a 3- to 6-fold decline in antimotility concentration compared to free Statistics [62].

### 2.1.2 Liposomes

Liposomes remain microparticles of spherical vesicles covering single or multiple configurations of bilayered membranes and were first described in 1965 [63]. It comprises of the outer layer of lipid and the core with hydrophobic or hydrophilic drug [64]. Liposomes can perform several roles by altering the composition of the lipid substrate the biophysical properties of living cells (eg. mobility and deformation) [65]. Liposomes was the first nano-scale medication permitted for clinical solicitation [66]. Through decades of study, liposome development has passed many centuries.

Compared to free paclitaxel, several paclitaxel liposomes obligate remained much greater anti-tumor efficacy and better bioavailability [67]. It has been proven that liposomal doxorubicin decreases cardiotoxicity and has similar effectiveness in BC [68]. Tang et al., [69] synthesized a series of liposome ligands that can recognize the sodium-dependent multivitamin transporter (SMVT) receptor over-expressed in BC cell. Further they modified four liposome (Bio-Bio-Lip, Bio-Lip, tetra-Bio-Lip and tri-Bio-Lip). They claimed such tri-Bio-lips took the greatest anti-proliferating impact on BC cell, according to the cytotoxicity and apoptosis review of paclitaxel-loaded liposomes. Additional research of *in vivo* targeting abilities was carried out using 4T1 tumour carrying BALB/c mouse. They concluded that the density of target molecules on the liposome surface would efficiently increase the capacity to target breast cancer. And the branching composition and spatial gap of biotin remains similarly obligate a substantial effect on the similarity of SMVT receptors. Ağardan et al., [70] prepared tamoxifen/raloxifene overloaded liposomes for oral management of BC. This research has been focused on the formulation of liposome of tamoxifen and raloxifene utilising dimethyl- $\beta$ -cyclodextrine (DM- $\beta$ -CD) or sodium taurocholate (NaTC) as a penetration enhancers. The liposomes of Raloxifene and DM- $\beta$ -CD demonstrated significantly greater permeability coefficient of almost 3.5 folds across Caco-2 lines. Tamoxifen DM- $\beta$ -CD liposome demonstrating a particle extent of  $244.7 \pm 8.1$  nm



demonstrated a greater reduction in tumour size (92.5%) and healing effectiveness (50%). Both these findings suggest that (SERM) drug-containing liposomes through permeation was safer for breast cancer oral therapy.

### 2.1.3 Polymeric nanoparticles

Polymer-based NPs remain added form of NP through unique essential preparations for the distribution of drug through various monomers [71]. On the basis of their structural organisation, PNPs can either be categorised as nanospheres (matrix type) or nanocapsules (reservoir type) [72]. For regulated and sustained drug delivery, Jadon et al., [73] developed docetaxel (DTX) captured lipid polymer hybrid nanoparticle (LPHNPs-DTX). LPHNPs-DTX remained primed and characterised for particle extent, zeta potential, PDI and drug release study. In-vitro cell line studies have demonstrated enhanced cytotoxicity and increased cellular absorption of docetaxel in breast cancer cell lines at a lower IC<sub>50</sub>. LPHNPs-DTX has been observed to reduce the tumour burden by a percentage as compared to free DTX.

### 2.1.4 Dendrimers

Dendrimers remain course of polymers with diverged macromolecules originating from the central core and obligate remained expedient towards nanomedicine. The macromolecules remain adaptable and biocompatible, with a three-dimensional branch structure [74]. Various forms of dendrimers are available depending on their structure and size. Winnicka et al., [75] has adapted glycosides-digoxin and proscillaridin A by 3polyamidoamine-dendrimer (G3PAMAM-NH<sub>2</sub>) in human BC cells. The findings showed such G3 PAMAM-NH<sub>2</sub> dendrimer conjugation increases the cytotoxicity in both MCF-7 and MDA-MB-231. In addition, conjugate-induced apoptosis was significantly higher in comparison to free digoxin and proscillaridin A. In order to enhance docetaxel distribution (DTX) to HER2-positive BC cells, Kulhari et al., [76] synthesised trastuzumab (TZ)-grafted dendrimers. Expending a heterocrosslinker, MAL-PEG-NHS, TZ bioconjugation on the surface of dendrimers was done. In vitro comparative experiments have shown that these targeted dendrimers are further selective and have improved anti-proliferation activity against HER2-positive MDA-MB-453 human BC cells. Furthermore *in-vivo* experiments have demonstrated substantial enhancement of the pharmacokinetic profile of DTX across the

conjugated nanosystem. MCF-7 BC cells were tested for *in vitro* study by utilising low-generation (G0, G1, and G2) PAMAM-like polymer [77]. Jain and co-workers [78] has advanced and evaluated usage of uncoated and PEGylated newer PAMAM dendrimers to deliver 5-fluorouracil anti-cancer drugs. In another research it was reported that when 5-FU, PEGylated polyamidoamine (PAMAM) dendrimers given in combination, it resulted in sustained and targeted *in vivo* and *in vitro* release of antitumor drugs in albino rats without any haematological disruptions. The research indicated that PEGylated dendrimeric methods was used as a nanoparticulate depot.

## 2.2 Inorganic Drug Delivery Approaches

Recently inorganic constituents as nano-carriers obligate demonstrated tremendous promise in DDS [79]. The developed inorganic nano-carriers system act as outlines in the system and remain adept of more drug loading and release, preserve intact blood supply mechanisms with virtuous biocompatibility and pharmacological features [80]. Inorganic NPs obligate the benefits of greater surface-to-volume ratios. They need a broad and certainly adjusted superficial conjugation interaction, simple and simplistic method of provision [81]. Inorganic nanoparticles, in addition to their managed drug release profile, shield the medication from deprivation and can decrease the occurrence of management and dosage of the medication. carbon-nanotubes (CNTs), gold NPs (AUNPs), quantum dots, silica NPs (SNPs) and magnetic NPs (MNPs) remain among the utmost extensively considered inorganic nanocarriers [82]. Even certain inorganic nano-carriers centered nanomedicine formulation remain under clinical evaluation [83].

Gold NPs (GNPs) remain practiced for distribution of chemotherapeutic medications for several cancers. They circulate within the tumour cells regardless of their small size and specificity. The GNP mixture was evaluated in the breast cancer cells for transferrin molecules. There was a greater cellular application of transferrin fragments connected towards GNPs relative to unbound fragments [84]. Zhang et al., [85] synthesised and developed herbal formulation of *Curcuma wenyujin* gold nanoparticles (CW-AUNPs) and studied its possible anticancer activity to BC cells. MTT assay inspected the cytotoxic activity of synthesised CW-AUNPs on MDA-MB231/HER2 cell lines. The apoptosis caused over CW-AUNPs remained examined



through intracellular ROS and caspase stages in CW-AuNPs processed with MDA-MB231/HER2 cell line. The findings truly demonstrate that the strong anticancer action of CW-AuNPs improves ROS in breast cancer cells. Jabir et al., [86] synthesized gold nanoparticles of Linalool by combining the composite through CALNN peptide and examined in in-vitro BC (MCF-7) cell lines. These novel synthesised compounds were confirmed by different analytical techniques.

Silver (Ag) is also swiftly attaining attention owing towards its reduced responsiveness as well as its vigorous outline and size-dependent capabilities. In order to acquire successful anticancer and immunomodulatory appearance, experiments encompassing Ag NPs as drug distribution vehicles utterly been proposed for instance nanoscale entity. Capecitabine bonding of silver particles in human BC cells (MCF-7) has been studied by Hepokura et al., [87] in an antiproliferative and proapoptotic evaluation. Various sizes of Ag NPs (5, 10, 15, 30 nm) have been synthesised. According to the findings, 10 nm-sized silver nanoparticles had the lowest toxic impact. The quantity of initial and late apoptotic cells in MCF-7 cells has been greatly increased by drug-bonded nanoparticles.

Superparamagnetic iron oxides (SPIOs) have been steadily researched for their outstanding supermagnetism, magnetic heating properties and improved magnetic resonance imaging (MRI). There are many benefits to the use of SPIONs with drugs to, including magnetic targeted functionalization, *in vivo* imaging, magnetic thermotherapy and simultaneous delivery of anticancer agents [88]. Panda et al., [89] Panda et al. has developed a docetaxel-loaded polymer superparamagnetic nanocarrier by hydrothermal and emulsion evaporation for the management of BC. The DTX loaded nanoparticles of iron oxide (DIONP) indicated round in outline with standard particle size distribution within a array of 160–220 nm. In the confocal microscopic and MTT experiments DIONP demonstrated higher internalisation performance and mild cytotoxicity in the MCF-7 cells. Compared to free drug, pharmacokinetic parameters have been shown to be enhanced. However, there is little information and needs to be researched around SPIOs' BC and metastatic lymph nodes injection.

Quantum dots (QDs), nano-sized fluorescent elements, adept of spotting and targeted delivery of molecules to in-vivo cancer cells [90]. QD

nanocrystals remain as one of the most preferable biological and biomedical system with tunable wavelength, great visibility, anti-photo bleach, and optical features [91]. A hybrid peptide was produced by Chih-Hsiang et al., [92] for concurrent cancer cell detection and healing. The hybrid peptide is constructed via the Doc-Coh interaction from two peptides. Through management of fusion peptide, HER2/neu-positive BC cells remained notorious and executed as a consequence of QD-emitted fluorescence and MNP-mediated hyperthermia.

### 2.3 Localized Drug Delivery Approaches

Conventional chemotherapy has been effective to some degree, the key disadvantages of chemotherapy include inadequate bioavailability, large dosage criteria, harmful side effects, low therapeutic indexes, non-specific targeting and production of multiple drug resistance [93]. The positive effectiveness and negligible side effects of managed drug delivery vehicles have been preferred. Localized drug delivery has a stronger effect than conventional medicine as a preventive alternative for early-stage cancers management.

Hydrogels of the NPs are the most commonly recognised formation for selective drug delivery in cancer. It is insoluble in aqueous liquids and can retain significant amounts of water. They facilitate the regulated release of a medication within the body. Tumor cell therapy hydrogels are mostly formed as microspheres or NPs. A novel, implantable hydrogel for local chemotherapy and reconstructed breast after the procedure was developed by Wang et al., [94]. Locally sustainable release of PTX was accomplished by local implantation of paclitaxel-nanoparticles-loaded double network (PTX-NPs-DN) hydrogel with favourable tolerability. The paclitaxel-nanoparticles-loaded double network hydrogel greatly increased the survival of mice in the tumour resection cavity after implantation. Segovia et al., [95] developed nanoparticle doped hydrogel for local and long-term distribution with strong in vitro and in vivo enactment in the distribution of siRNA to mice model treatments of breast cancer. Encapsulating in oligopeptide-terminated poly( $\beta$ -aminoester) (pBAE) nanoparticle enables siRNA safety and high transfection performance. The mixture of oligopeptide-terminated pBAE polymer and decomposable hydrogel demonstrates increased transfection performance in vivo relative to the utmost effective currently

accessible transfection components. These observations demonstrate the importance of utilising compound structures to produce these extremely promising small molecules effectively to fight cancer.

Nanofibre scaffolds is one of the most modern and professional drug carriers that revolutionise the nanomedicine sector due to their high surface volume. A nanofibre is a crosslinked polymer with a tensility and chemical characteristics. For the preparation of nanofibers for uniform drug delivery, degradable polymers like PLGA, chitosan, PEG, PVA, PLA, PCL and polyethylene oxide remain practiced [96]. Sedghi et al., [97] has developed and measured the ability of modern chitosan derivative nanofibers for the preclusion of local recurrence of BC. In this research, nanofibers improved their anti-cancer properties and minimise their side effects. Excellent anticancer action against 4T1 cells have been reported with no cytotoxicity in normal cells. In the MCF-7 BC cell line, curcumin-loaded PCL nanofibers were examined and demonstrated 15 % more cytotoxicity relative to the commercial medication [98].

#### **2.4 Receptor-Based Drug Delivery Strategies**

If BC cells obligate estrogen receptors, the cancer remains entitled ER-positive BC. Approximately 70% of BC remain ER-positive. If BC cells have progesterone receptors, the cancer remains termed PR-positive breast cancer. Approximately 65% of these stand similarly PR-positive. If the cells do not have either of these 2 receptors, the cancer remains termed ER/PR-negative. Approximately two-thirds of BC remain ER and/or PR positive. The proteins in the cell entitled cyclin-dependent kinases (CDKs), predominantly CDK4 and CDK6. Blocking these proteins in hormone receptor-positive BC cells aids stop the cells from separating [99].

The EGFR (Epidermal growth factor receptor) remains solitary of the foremost oncogenes notorious in a diversity of human malignancies comprising BC. Amid the utmost prominent cancer molecular targets towards the EGFR/ErbB clan: EGFR (similarly notorious as ErbB1 and HER1), HER2 (similarly notorious as ErbB2 and HER2/neu), ErbB4 (similarly notorious as HER4) and ErbB3 (similarly notorious as HER3) [100]. HER2, such remains overexpressed in 20% to 25% of BCs, remains

the utmost well recognized therapeutic aim in BC.

Some BCs considerable of a protein (receptor) entitled HER2 on the superficial of their cells. This remains termed HER2-positive BC. HER2 stands a sort of protein notorious as a kinase. Kinases remain proteins impart signals (aforesaid as significant the cell towards grow). The further HER2 protein reassures the cancer cell towards division and propagate. Amid 15 and 20 obtainable of each 100 women through BC (15 to 20%) have HER2-positive cancer [101]. Cancer as such does not obligate receptor for either HER2 or the hormones oestrogen and progesterone remains entitled triple negative breast cancer (TNBC). It distresses up to 1 in 5 women (15 to 20%) by BC and remains further collective in younger women [102].

The development of BC is controlled through many receptors and the receptor reticence offers a novel path for cancer remedy. Receptor targeting tests remain practiced in clinical trials in women through metastatic BC. A number of researches based on HER-2, EGFR, VEGFR and IGF-IR receptors, such demonstrated clear goals for cellular breast cancer [103]. Agus et al., [104] identified an approach that uses a monoclonal antibody, 2C4, to target the function of ErbB2 as a coreceptor that sterically impedes the conscription of ErbB2 into ErbB ligand facilities. 2C4 remains good for blocking heregulin-mediated ErbB3-ErbB2 signalling. Valabrega et al., [105] blocked the receptor with antibodies to enhance the therapy of tumours resistance to trastuzumab. Trastuzumab has demonstrated clinical efficacy in HER2-overexpressing both metastatic and adjuvant conditions. Tyrosin-kinase receptor, such as lapatinib, inhibits the expression of 30 % of breast cancers of EGFR (ErbB1) and HER-2 (ErbB2). The Phase II study reported a 33% retort level following management of HER-2-positive metastatic BC through lapatinib.

The EGFR expression has been found to be associated through an amplified number of replicas of the gene and protein overexpression in BC. PR-negative, ER-negative, HER-2 negative (triple-negative) BC patients reported an elevated gene copy number of EGFR genes and protein over-expression. Nguyen et al., [106] targeted nanomedicine through humanised anti-EGFR scFv (NM-scFv) has been advanced for transmission of siRNA to TNBC cell. NV-scFv remained centered on a DylightTM680 super-

paramagnetic nanopartment (SPION), a PEG level and a humanised anti-EGFR scFv. This improvement resulted in a double advantage of improved cellular internalisation by a factor of 2.0 over a 24-hour incubation cycle and a reduced availability of proteins indicating increased stealthiness. The potential clinical approach for metastatic breast cancer may either be targeted at endothelial growth aspect only or in conjunction through a aim agent.

### 3. SIGNALING PATHWAYS AND ONCOGENE PARTICIPATION IN BREAST CANCER

At the intracellular level, the links across stimuli and ion or receptor networks might get trigger distinct ensuing signalling routes, like Phosphoinositide-3-kinase–protein kinase B (PI3K/AKT) and Mitogen-activated protein kinase (MAPK) and Ca<sup>2+</sup> signalling route, as demonstrated in Fig. 3. The consistent signaling pathways might prompt the BC cells to thrive and endure beneath a assorted situation through several down-regulated and up-regulated proteins and represented in Table 3 [107]. The ascertain of the tumor suppressor genes and oncogenes prevailing BC signaling conduits. It remains an vital aim in healing mediation of BC.

#### 3.1 Mitogen-Activated Protein Kinase (MAPK) Pathway

MAPKs is a protein with major function in conveying and enhancement of extracellular signals. The MAPK signalling of the activation of

the ERK pathway also remains activated by ligand binding through the membrane receptor, particularly as the tyrosine kinase receptor. In the primary human breast cancer tissue, hyperexpression of MAPK persisted parallel to the benign component identified with metastatic latent disease [105,2]. The reduction in BC cell proliferation and transferring was revealed by revisions to down-regulate the expression of MAPK duty [105].

#### 3.2 PI3K/AKT Pathway

The important protein in response to the signals of both the receptor tyrosine kinase and the AKT is Phosphatidylinositol 3-Kinase (PI3K) [106]. Several reviews have found that 70 % of breast cancers have deregulated and mutated genes in this pathway [107]. PI3K signalling mechanism can be triggered when stimulated with ligand attaches to tyrosine kinase receptor. As a consequence, the message is sent to the AKT route, specific to the mTOR signaling route. Cellular roles, such as replication and survival, are maintained through phosphorylation of AKT (pAKT).

#### 3.3 Calcium Signaling Pathway

Calcium ions (Ca<sup>2+</sup>) are still regarded a penetrating cell signal and among the most important second messengers in cell signaling. Ca<sup>2+</sup> is liberating in the cytoplasmic matrix form either internal reserves, like the ER (endoplasmic reticulum) and various cell membrane-associated channels. Furthermore, Ca<sup>2+</sup> has a role in cell

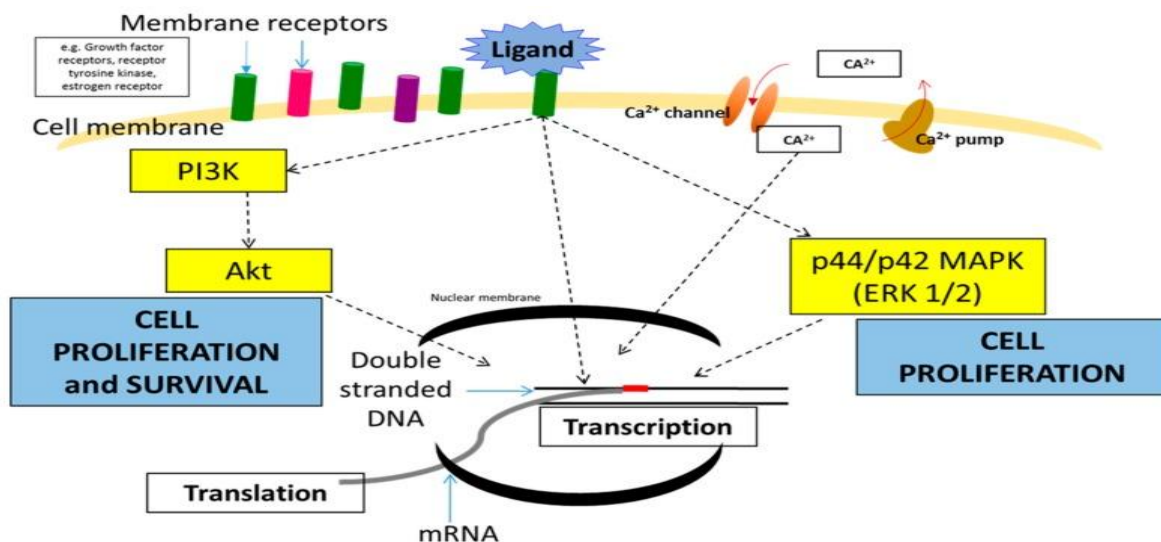


Fig. 3. Signaling pathways in breast cancer (Kamaruzman et al., 2019)

**Table 3. Signaling pathways in breast cancer**

Pathway Name	Signaling	Pathway activation	overexpression	Reference
Mitogen-Activated Protein Kinase (MAPK) Pathway	conveying and intensifying the extracellular signals	triggered by the bind of ligand through the cell membrane receptor	the decline in BC cell multiplying and migration	[108]
Phosphatidylinositol 3-kinase (PI3K) /AKT Pathway	signals from a similar receptor tyrosine kinase that point to AKT	transfers the data to the AKT conduit, certainly as the mTOR communicate conduit	In 33% of cases of ductal carcinoma in situ and 38% of cases of invasive BC	[109,110]
Calcium Signaling Pathway	messengers in cell signaling	CDK2 and CDK4 are cyclin-dependent kinases that help the cell cycle progress from G1 to S phase.	increase in propagation, migration, and assault of the cancer cells	[111]
Notch Signaling Pathway	Notch receptor on the contiguous cell and interface of the DSL(Delta/Serrate/ LAG-2) ligands on one cell	associates thru the cellular advance, certainly as spread, hypoxia,apoptosis, angio-genesis, epithelial to mesenchymal transition, cancer stem cell action, and metastasis	the endurance of BC cells valor remain persuaded via AKT pathway activation	[112,113]
Hedgehog Signaling Pathway	conveys evidence to embryonic cells obligatory for proper cell diversity	The triggering of smoothened (Smo), 7 transmembrane protein like extra roused multi-complex proteins such enclosed Gli protein	hostile prognosis and subsistence of the BC cells	[114]
JAK/STAT Signaling Pathway	transmits data to the cell nucleus from chemical sources outside the cell	intricate stem cell conservation, contribute in the practice of inflammatory retort and hematopoiesis	phosphorylated-STAT3 and STAT3stood upregulated in 69.2% of BC tumors	[115]
Anti-Apoptotic Signaling Pathway	response to environmental and cellular affronts	Activation of growth factor receptors, most notably HER2.	Inhibits the pro-apoptotic proteins like BAX and BAD, induces apoptosis.	[116]

growth. It is a complex that regulates the advancement of the cell cycle from phase G1 to phase S by activating cycline-dependent phases (CDK4 and CDK2) [108]. The GTP-binding protein is overexpressed. Rap2B raised the amount of intracellular calcium, subsequently preserving the phosphorylation of ERK1/2 in breast cancer cell lines Bcap-37 and MDA-MB-231.

### 3.4 Notch Signaling Pathway

A notch signalling pathway would be formed when the DSL (Delta/Serrate/LAG-2) ligands from one cell interact with the Notch receptor on an adjacent cell [109]. Notch receptors and their ligands tended to be over-expressed in breast cancer. CyclinA, cyclinB, and cyclinD1 expression have been shown to be upregulated,

while BC cell survival may be induced by the Notch signalling pathway by stimulation of AKT pathways [110].

### 3.5 Anti-Apoptotic Signaling Pathway

MCL-1, BFL-1/A1, BCL-XL, BCL-2 and BCL-W are all anti-apoptotic proteins of the B-cell lymphoma 2 (BCL2) family. The BCL-2 protein is important for cancer cells to survive for a long time [113]. By stimulating PI-3 kinase signals, growth factor receptors such as HER2 might influence BCL-2 expression.

### 3.6 JAK/STAT Signaling Pathway

Intracellular proteins include Janus kinase (JAK) and transcription inducers and activators of transcription (STAT). The transmembrane receptor coordinates the delivery of signals to the core for DNA transcription and gene expression. The silencer of cytokine transmission proteins is the regulator of the JAK/STAT/JAK/STAT negative reaction loop is the suppressor of cytokine signalling proteins (SOCS). The key tasks as viable STAT inhibitors while STAT enhances SOCS gene transcription [112].

### 3.7 Hedgehog Signaling Pathway

Cell division, stability, diversity, cell survival, regeneration, and stem cell conservation are all common practices and are regulated by the Hedgehog signalling pathway [111]. Many basal-like breast cancers (BLBC) are immune to chemotherapy therapies and have a triple negative phenotype of essential receptors (ER-, PR-, and HER2).

## 4. BIOCHEMICAL APPROACHES

Fourier transform infrared (FTIR) spectroscopy remains a modest, swift, reagents-free biochemical implement such delivers evidence on the total molecular alignment of biological sections. FTIR spectroscopy remains a prevailing investigative biochemical and imaging process. It remains intricate to detect a variation in a precise molecule owing to the overlying groups and the adequately of enormous molecules such constitute biological illustrations. FTIR spectroscopy devours remained one of the beneficial for the exposure and report of an extensive variability of cancer cells and tissues [117]. FTIR spectroscopy of peripheral blood mononuclear cells (PBMCs) such remained then

practiced to display the illness through chemotherapy [118].

### 4.1 FTIR Spectroscopy

All spectroscopy revisions should achieve through the Nicolet Centaurus FTIR microscope fortified by a liquid-nitrogen-cooled mercury-cadmium-telluride indicator combined towards Nicolet iS10 OMNIC software (Nicolet, Madison, WI). Towards accomplishing a great signal-to-noise ratio (SNR), 128 co-added probes stood poised in respectively extent in the 700 to 4000  $\text{cm}^{-1}$  wavenumber section. At a spectral determination of 4  $\text{cm}^{-1}$  (0.482  $\text{cm}^{-1}$  data spacing), respectively spectrum encompasses 6845 data points. The extents of the quantity site stood 100  $\mu\text{m}$  X 100  $\mu\text{m}$ . Extents remained achieved in transmission mode at least 5 times at diverse adverts in apiece sample of plasma.

### 4.2 Immunohistochemical Staining Assay” or an “Immuno Histo Chemistry (IHC)

IHC remains practiced to apprehend the delivery and positioning of proteins in diverse portions of a biological tissue. IHC identifies precise antigens in conserved tissue segments expending an applicable antibody marking approach. Illustrations remain poised, stable towards sustained cell morphology, tissue architecture and antigenicity of target epitopes, and formerly partitioned. A variability of antibody staining outlines can create revealing IHC pictures. Having an antibody conjugated towards a fluorophore (immunofluorescence) remains a collective recognition process [119].

If the cancer remains considered “estrogen-receptor-positive” (ER+), its cells obligate receptors for the estrogen hormone. Such resources particularly the cancer cells possible accept signs from estrogen towards uphold advance. If the cancer remains progesterone-receptor-positive (PR+), its cells obligate receptors for the progesterone. This hormone might formerly support the advance of the cancer.

### 4.3 HER2/neu Test

Analogous towards the hormone receptor assessment, the HER2/neu assessment aspects for a precise generous of protein such remains institute through assured sorts of cancer cells

and the gene which creates it. The prescribed label of such gene remains the human epidermal growth factor receptor 2, and it marks HER2 proteins. These proteins remain receptors on breast cells. BC patients, the HER2 gene isn't effective suitably [120]. It marks an surplus quantity of copies of itself in a procedure notorious as "HER2 gene amplification." Then these further genes initiate the cells towards sort too sundry HER2 receptors, aforesaid remain entitled "HER2 protein overexpression."

#### 4.4 Steroid Sulfuration

In humans the enzyme accountable for deconjugation of sulfated clusters remains collective towards mutually androgenic and estrogenic steroids. This enzyme remains steroid sulfotransferase (STS), correspondingly designated aryl sulfotransferase. These sulfated steroids remain anticipated towards act as a mere of precursor steroids in tissues, aforesaid as the breast and the prostate, adept of deconjugating the sulfate moiety from the steroid mainstay. In BC, revisions have an intensive on polymorphisms in UGT1A1, SULTE1/EST, and SULT1A1. For UGT1A1, the popular of revisions probing genetic distinction have gaged the impression of variations allied by a lesser rate of enzyme transcription in vitro. The revisions revealed an association amid the little action variant and an amplified risk of premenopausal BC transversely a quantity of ethnic populaces and in adding an association by cancer mark, estrogen negativity and amplified mammographic density [121].

### 5. GROWTH FACTOR RECEPTORS AND BREAST CANCER

An integral monitoring feature that subsidises cell proliferation and survival is the expression of growth factor receptors (GFRs). Growth factors, cytokines, and hormones are examples of ligands.

#### 5.1 Insulin-Like Growth Factor 1 Receptor (IGF1R)

IGF1R is a heterodimeric membrane receptor made up of subunit binding site -ALPHA and subunit ligand binding-BETA which is connected with the domain of tyrosine kinase. The association of IGF1 to the IGF1R causes autophosphorylation of tyrosine kinases, which is

necessary for downstream indication to cascades including the PI3K/AKT and MAPK pathways to be activated. IGF1R-coordinated members of the IGF family seemed to be highly expressed in breast cancer tumours and were linked to cancer development [116].

#### 5.2 Transforming Growth Factor-Beta Receptor (TGF- $\beta$ R)

TGF- $\beta$ R has the protein ligand, that is also accessible through an extracellular matrix (ECM). There are namely 3 types of TGF- $\beta$ R protein namely, TGF- $\beta$ R1, TGF- $\beta$ R2, and TGF- $\beta$ R3. The ligands TGF $\beta$ 1 and TGF $\beta$ 3, once triggered, binds itself to TGF- $\beta$ R2, while the TGF $\beta$ 2 is more symmetrical to TGF- $\beta$ R3. The binding of TGF-R2 with its ligand may aid in TGF-R1 activation [117].

#### 5.3 Human Epidermal Growth Factor Receptor 2 (HER2/ERBB2)

HER2 is still one of the most well-known members of the tyrosine kinase receptor class inherited by the ERBB2 gene. In breast cancer cells, circuit formed between HER2 and other cell membrane receptors such as ER, IGFR, and EGFR could promote downstream signaling via MAPK and PI-3 kinase pathways [121]. It indicates the benefit of controlling the genes key for therapeutic cross-talks. N-glycosylation of the epithelial cell adhesion molecule (EpCAM) observed in parallel with HER2 in breast cancer tissues. Furthermore, it has been discovered that this event promotes cancer cell multiplication while inhibiting apoptosis [122].

#### 5.4 Epidermal Growth Factor Receptor (EGFR)

EGFR is an integral membrane protein receptor that lies outside the tyrosine kinase family of receptors. It is frequently stimulated by the EGF, and serves as ligand and reduces signal cascades, such as Ras/Raf, MAPK and PI3K/AKT. It can be activated in order to regulate cell growth and survival [114]. It is among the receptors that is related to an initiator of breast cancer. And the overexpression of EGFR is also correlated with bad prognosis. The expression of EGFR also acts as the breast cancer biomarkers such as the androgen receptor and the protein Ki67 [115].

## 5.5 Vascular Endothelial Growth Factor Receptor (VEGFR)

VEGFR is a tyrosine kinase sensory receptor associated with seven immunoglobulin (Ig)-like domains. It is likely to exist in the extracellular area of the cell [118]. The relationship between VEGF and VEGFR has also been related to blood vessel angiogenesis or vasculogenesis in tumours. The rise in breast tumours in the murine model has been focused on the expression of VEGFR1 [119]. VEGFR2 remained inveterated for the function of angiogenesis and inhibitors of breast cancer [120].

## 6. CONCLUSION AND FUTURE PROSPECT

Breast cancer is a heterogeneous disorder attributable to dynamic associations between multiple origin cells and oncogenic activities. Standard cancer treatment methods such as chemotherapy and radiation may destroy cancer cells but are often correlated with collateral tissue harm and variable patient-to-patient therapy effectiveness. However these therapy methods can not regulate metastatic cancers that have arisen in different organs. As a consequence, the search for new treatment methods remains an unmet need. Meanwhile, utilising innovative approaches and combining genomic and proteomic advances to expand breast cancer care, a newer method, nanomedicine, is progressing toward personalised medicine. Due to its greater surface to volume ratio, pharmaceutical nanocarriers are especially essential in the design of DDS which boost biodistribution and PKs. Different forms of nanocarriers were studied, allowing researchers to resolve shortcomings of traditional chemotherapy through amassed the solubility of the free medication and declining toxicity towards vigorous tissues. With respect to nanoparticle-related DDS, we emphasise the regulation of the tumour environment based on nanoparticles. The combination of nanotechnology goods with therapeutic agents, such as nanoparticles, devours recently generated a modern beneficial trend such would otherwise not remain feasible.

With growing research, different forms of NPs showed enhanced distribution properties and increased attention. Further studies into the molecular aspects of particular cancers can contribute to more specific research directions for these medications. One of the key problems of

the recent development of nanotechnology to be utilised successfully for the treatment of different tumours is the expansion of new-generation nanocarrier medicines. This extension will validate the successful tumour targeting by interfering with the attached surface ligand and receptors in the cells and tissues chosen. In addition, the development of immunomodulatory factor-charged NPs can boost the efficacy of immunotherapy vaccines. Furthermore, we concentrate on the toxicity of nanoparticles and the ligand immunogenicity factors of clinically efficient nanocarriers for anti-cancer medicines.

## DISCLAIMER

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

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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