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INNOVATIVE STRATEGIES FOR TARGETED BREAST CANCER TREATMENT: BEYOND CONVENTIONAL THERAPIES

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Abstract

Breast cancer is a worldwide health challenge, with alarming data highlighting its widespread effects. The significance of this condition is quantified by its prevalence and the difficulties it presents to healthcare systems, requiring a detailed examination of its epidemiology and effects. Contemporary breast cancer interventions, encompassing surgery, chemotherapy, radiation therapy, and targeted therapies, have markedly advanced in enhancing patient prognoses. Nonetheless, they possess limitations, frequently resulting in detrimental consequences and the emergence of drug resistance. This thorough overview examines the intricate topography of breast cancer, encompassing its occurrence, contemporary treatment methods, and the intrinsic limitations of current therapeutic strategies. It elucidates the potential of nanotechnology, including both inorganic and organic nanoparticles, to selectively transport therapeutic medicines to tumour locations in the fight against breast cancer. The study examines developing medicines, their related obstacles, and the future potential of targeted drug delivery in breast cancer treatment.

INTRODUCTION

Healthcare systems throughout the globe face a significant challenge from cancer, a complicated and terrible group of illnesses marked by unchecked cell proliferation and tissue invasion [1,2]. Of the many cancer forms, breast cancer is one of the most common and extensively researched. It has a variety of subtypes according to molecular traits [3,4]. The death rate from breast cancer among women with a diagnosis was around 29.1% in 2022, with 670000 deaths recorded out of 2.3 million cases [4].Breast cancer is still a major worldwide health problem, despite improvements in patient outcomes brought about by early diagnosis and treatment advances [6]. There are still issues including late-stage diagnosis, hereditary predisposition, and restricted access to healthcare in underprivileged areas [7, 8].

Understanding the molecular heterogeneity of breast cancer is essential for developing individualised

treatment plans since the disease has several facets [9]. The molecular complexities of breast cancer have been clarified by recent research, which has identified many subtypes with distinctive clinical characteristics and treatment outcomes [10]. For HER2-positive breast cancer, the discovery of molecular markers such hormone receptors and the presence of the human epidermal growth factor receptor 2 (HER2) has transformed therapeutic strategies and made it possible for targeted medicines like Herceptin [11]. But even with these developments, late-stage diagnosis is still a major worry [12]. By creating sophisticated imaging methods and screening procedures, attempts have been made to increase early detection [13]. Genetic predisposition is also important for assessing and preventing breast cancer risk, as shown by BRCA1 and BRCA2 mutations [14]. Depending on the kind and stage of the tumour, current treatment methods include a multidisciplinary approach that includes hormone therapy, radiation therapy, chemotherapy, and surgery (mastectomy and lumpectomy) [15]. Even while these methods have significantly improved patient outcomes, there are still certain disadvantages [16]. While surgical procedures pose the danger of organ damage and subsequent problems, chemotherapy and radiation treatment can cause crippling side effects including nausea and exhaustion [17]. Furthermore, conventional treatments may not be very effective, especially in cases of advanced or metastatic illness, and they may unintentionally increase cancer cell resistance. Additionally, patients' financial stability and general well-being may be severely impacted by their intrusive nature and high expense [18]. Traditional treatments are still essential parts of cancer therapy, however, and they often work in tandem with newly developed immunotherapies and targeted medicines to improve treatment results. Adjuvant radiation therapy, for example, has significantly raised survival rates and reduced the likelihood of recurrence [19]. Immunotherapy has become a viable therapeutic option for breast cancer in recent years. Immune checkpoint inhibitors, which use the immune system to fight cancer cells, include programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors. These inhibitors are being studied in clinical studies (Fig. 1) [20]. Optimising therapeutic results, personalised medicine, driven by genetics and biomarker research, enables tailored therapy regimens based on each patient's distinct cancer profile [21].

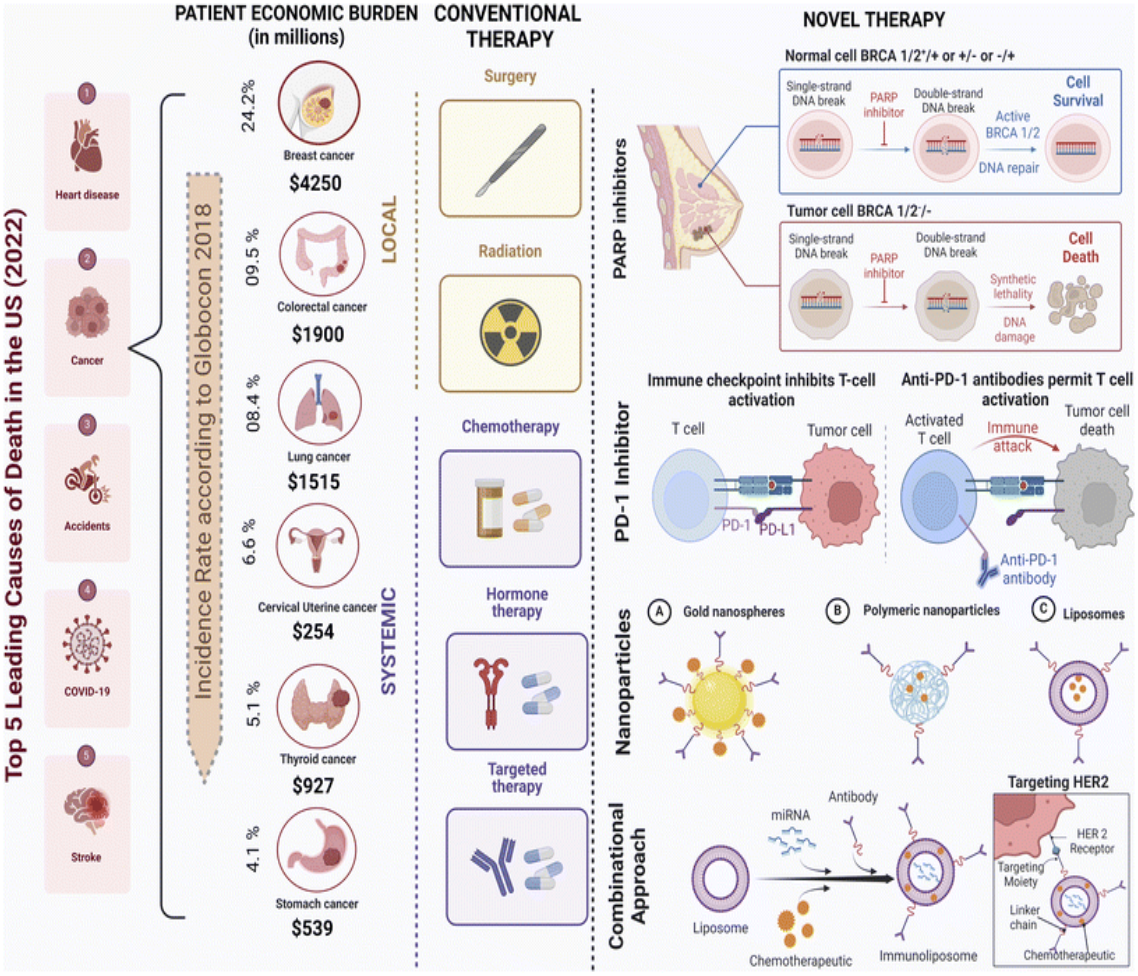

Figure 1: Cancer's worldwide burden with advancements in targeted treatments.

2. Significance of targeted drug delivery in breast cancer:

For a variety of reasons, breast cancer is more complicated than many other types of cancer. The table below highlights Pakistan's global position in terms of various cancer types. Rankings marked in red indicate cancers that are spreading quickly in the country, while those in purple suggest the disease is becoming less common. Based on this data, Breast cancer appears to be on the rise in Pakistan.

Pakistan cancer rank by type:

Type	Rate	World Rank
Breast Cancer	19.33	58
Oral Cancer	9.40	10
Lung Cancer	7.81	121
Stomach Cancer	6.66	97
Cervical Cancer	6.56	78
Esophagus Cancer	6.17	42
Lymphomas	4.85	106
Colon-Rectum Cancer	4.08	149
Luekemia	3.61	112
Bladder Cancer	2.86	80

Liver Cancer	2.69	172
Prostate Cancer	2.53	164
Ovary Cancer	2.36	81
Other Neoplasm's	1.57	147
Pancreas Cancer	0.90	172
Uterin Cancer	0.51	142
Skin Cancer	0.31	170

So, this challenge should be addressed as soon as possible and studies reveal that breast cancer is very heterogeneous, with several genetic subtypes, including triple-negative breast cancer (TNBC), HER2-enriched, luminal A, and luminal B, each exhibiting unique biological behaviours and therapeutic responses [3,10]. Creating efficient treatment plans that are suited to each patient is made more difficult by this variability. For breast cancer, targeted medication administration is a game-changing strategy with important ramifications for enhancing therapeutic results [26]. This strategy is especially important since it tackles the problems with traditional radiation and chemotherapy, which can cause serious side effects and systemic toxicity [27]. Novel drug delivery systems, including liposomes and nanoparticles, have been made possible by advances in nanotechnology. These systems may encapsulate chemotherapeutic medications or other targeted agents and release them selectively inside the tumors microenvironment [28]. These nanocarriers may increase medication concentration at the tumour site and reduce off-target effects by improving drug stability, bioavailability, and circulation times [29]. Additionally, the treatment of breast cancer has been transformed by the development of targeted medicines such small molecule inhibitors and monoclonal antibodies [12]. Trastuzumab and pertuzumab, two HER2-targeted monoclonal antibodies (mAbs), have been authorised as adjuvant therapy for HER2+ breast cancer and metastatic breast cancer within the last 20 years. The mainstay of treatment for HER2+ breast cancer is trastuzumab, an early development in targeted oncology therapy. Trastuzumab works in a number of ways, including as via blocking downstream signalling pathways such the PI3K-AKT pathway and by inhibiting HER2 receptor dimerisation, internalisation, and disruption through antibody-dependent cellular cytotoxicity (ADCC) [30,32]. By interfering with DNA repair in cancer cells, PARP inhibitors such as olaparib take advantage of synthetic lethality with BRCA mutations, selectively targeting BRCA mutant cancer cells while preserving healthy ones [33]. The first authorised angiogenesis-targeting monoclonal antibody, bevacizumab (Avastin®), has had a major influence on cancer treatment. It works by preventing the activation of VEGF signalling pathways by suppressing vascular endothelial growth factor A (VEGF-A), a crucial component of angiogenesis. Because of this, it is now a key element in the treatment of solid tumours driven by angiogenesis, such as HER2-negative breast cancer and triple-negative breast cancer (TNBC) [34]. Considerable research has shown the efficacy of tailored medication delivery systems. Aptamer-functionalized liposomes significantly lower the dosage of doxorubicin and enhance therapeutic advantages by facilitating targeted transport to Her2-positive breast cancer cells, as reported by Chowdhury et al [35]. A study conducted in 2021 by Ghosh et al. showed that the targeted transport of curcumin using mesoporous silica nanohybrids modified with hyaluronic acid causes cancer cell death through mechanisms that include cell cycle arrest, the production of reactive oxygen species (ROS), and the modulation of both the Bax-mediated apoptotic pathway and NF-κB [36]. Furthermore, Cao et al. studied triple-negative breast cancer in 2023 and used MTX-PEG-modified CG/DMMA polymeric micelles to administer doxorubicin. This method showed improved anti-tumor activity and triggered autophagy [37].

These therapies concentrate on the molecular pathways and receptors that contribute to the development and metastasis of breast cancer. Finding

genetic abnormalities, signalling pathways, and gene expressions that affect tumour formation is a key component of the relationship between molecular processes and therapy for breast cancer [38]. The goal of targeted treatments that target certain molecular targets, such as the PI3K/AKT and HER2 pathways, is to enhance the efficacy of therapy by interfering with important carcinogenic pathways [39]. Optimised therapeutic results may be achieved by customising therapies according to the molecular subtype of the tumors [40]. When combined with platforms for targeted drug delivery, they may lead to highly targeted and effective tumor therapy [11]. All things considered, tailored medication delivery is a promising approach to breast cancer treatment that may lead to better patient outcomes, less side effects, and more effective treatment. Our knowledge and use of this novel treatment strategy for breast cancer are being furthered by ongoing research and development in this area, which is aided by studies on nanocarrier design, targeted therapeutic mechanisms, and clinical trials [25].

Research and therapy for breast cancer are constantly being shaped by scientific developments, as shown by molecular characterisation, targeted medicines, and creative drug delivery methods. With the ultimate goal of improving patient care and outcomes, ongoing attempts to improve early diagnosis, understand the complexity of tumor heterogeneity, and provide more accurate and potent medicines hold out a lot of potential for the future [26]. This study tackles the ever-changing field of breast cancer research and its crucial implications for bettering patient treatment and outcomes by looking at recent advancements and the present level of knowledge [41].

3. Approaches of targeted drug delivery:

As a result of the need for more accurate and efficient treatment methods, targeted medication delivery has emerged as a key component of illness therapy. Fundamentally, it aims to minimise the harmful effects of anticancer drugs on healthy tissues while maximising their therapeutic effectiveness. This strategy depends on a thorough understanding of the molecular targets and biomarkers that are closely linked to breast cancer [27]. Breast cancer is a complicated collection of illnesses with unique molecular profiles, rather than a single disease. Because patient responses to medicines might differ greatly, this variability presents a therapy problem. As a result, identifying particular biological targets and indicators is essential for customising therapy plans [3].

3.1. Molecular targets and biomarkers

The treatment of breast cancer has been transformed by molecular targets and biomarkers. The selection of hormonal treatment is influenced by the presence or lack of hormone receptors, such as the oestrogen receptor (ER) and progesterone receptor (PR) [41]. Another crucial biomarker is HER2, which has aided in the creation of HER2-targeted treatments like Herceptin, significantly enhancing the prognosis of patients with HER2-positive breast cancer [42]. Additionally, the complex molecular subgroups of breast cancer, including triple-negative, HER2-enriched, luminal A, and luminal B, have been revealed by genomics advances (Fig. 2) [43]. Every subtype has distinct clinical behaviours, genetic markers, and therapy responses. Treatment choices are guided by biomarkers linked to these subtypes, guaranteeing a more individualised and successful strategy [3, 43].

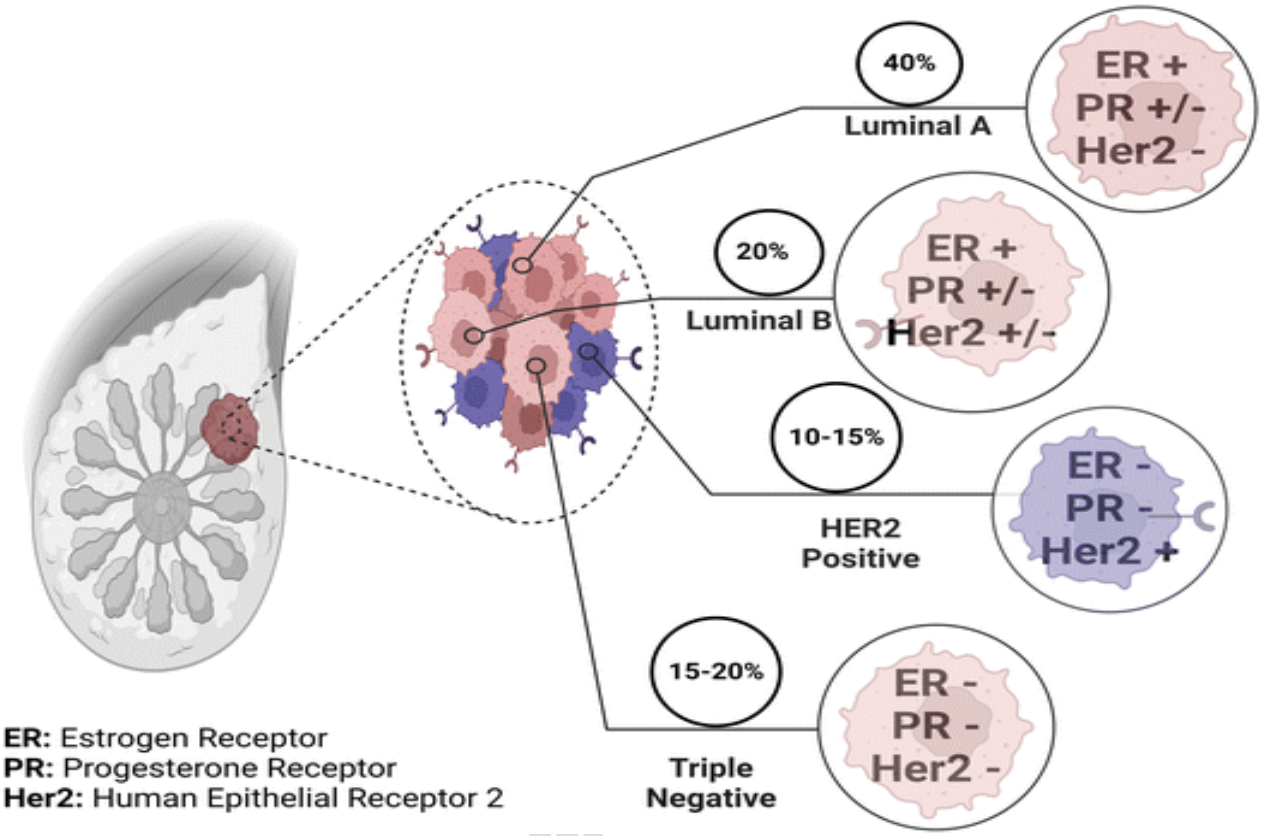

Figure 2: Molecular subtypes of breast cancer. Breast cancer is classified into four major molecular subtypes based on the expression of specific receptors, including estrogen receptor (ER), progesterone receptor (PR), Human Epidermal Growth Receptor 2 (HER2), and the absence of all three receptors (triple negative).

3.2. Targeting strategies for breast cancer:

By reducing systemic toxicity and perhaps increasing therapeutic effectiveness, targeted drug delivery systems have completely changed the way that breast cancer is treated [46]. This may be designed to get around the processes of drug resistance that often make breast cancer therapy less successful [47]. Targeted drug delivery offers great promise for overcoming medication resistance by improving drug delivery to resistant cancer cells or by using combination treatments that target many resistance mechanisms [11]. This section highlights new developments and their therapeutic consequences as it explores different targeting tactics to improve medication delivery, especially to breast cancer cells.

3.3. Passive targeting through enhanced permeability and retention (EPR) effect:

In breast cancer treatment, passive targeting is based on a basic phenomena called the increased permeability and retention (EPR) effect (Fig. 3a). This impact takes use of the unique properties of the tumour microenvironment [48]. Breast cancer is one of the numerous solid tumours that often have aberrant blood arteries feeding the tumour with nourishment. Because of their uneven form and leakiness, drug carriers and nanoparticles may passively infiltrate the tumour tissue [49].

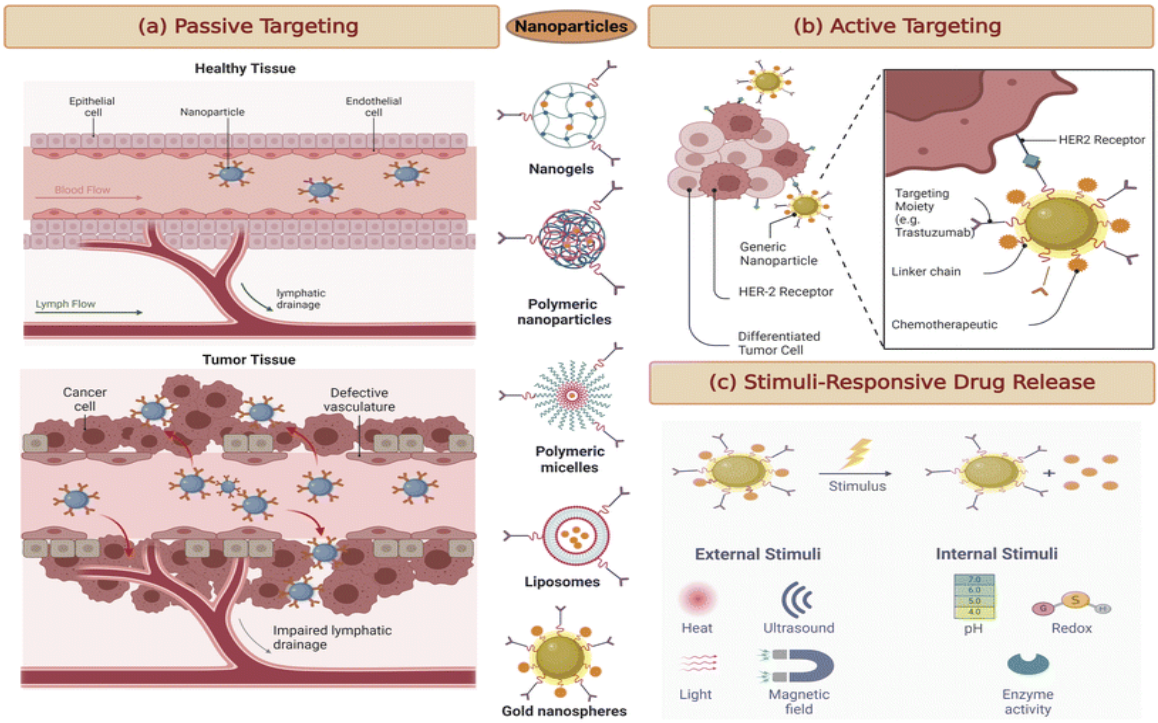

Figure 3: A schematic representation highlighting three distinct approaches in drug delivery systems. (a) Enhanced Permeation and Retention (EPR), (b) active targeting with ligands or antibodies and (c) stimuli-responsive drug release.

Because of the tumor's inadequate lymphatic drainage, these nanoparticles have a tendency to collect once inside. The lymphatic system, which removes waste materials and fluid from tissues, is often weakened in cancer, which makes it more likely that nanoparticles will remain in the tumors microenvironment [50].

Optimising the design of drug carriers and nanoparticles to enhance the EPR effect has been the focus of recent study. To maximise medication delivery to breast tumors and reduce off-target effects, parameters including particle size, surface charge, and drug release patterns are meticulously adjusted [51]. Researchers want to increase the effectiveness and selectivity of breast cancer therapy by taking use of the EPR effect.

3.4. Active targeting using ligands and antibodies:

By using particular molecules, such as ligands, antibodies, or peptides, to actively direct drug carriers to their intended target cancer cells, active targeting techniques for breast cancer treatment adopt a more accurate approach (Fig. 3b) [52]. These targeting moieties were chosen because they have a high affinity for receptors that are often overexpressed on the surface of cancer cells [53]. Drug delivery may be accurately targeted to the tumors location by conjugating these targeting ligands to drug carriers like liposomes or nanoparticles. By minimising off-target effects, this method protects healthy tissues from the damaging effects of chemotherapy or other therapeutic drugs [54].

The creation of antibody–drug conjugates (ADCs) for the treatment of breast cancer is one of the field's most notable developments. Monoclonal antibodies that precisely identify cancer cell surface receptors connected to strong cytotoxic payloads make up ADCs. This combination enables a very effective and targeted treatment strategy in which the antibody targets the cancer cell directly with the cytotoxic medication, killing it while leaving healthy cells unharmed [55].

3.5. Stimuli-responsive drug delivery systems for breast cancer:

One of the most innovative approaches to breast cancer treatment is the use of stimuli-responsive

medication delivery devices. Only when certain circumstances within the tumor microenvironment are met will these systems release therapeutic chemicals (Fig. 3c) [56]. Variations in pH, temperature, or enzyme activity specific to cancer cells are examples of such circumstances. In order to ensure accurate medication release inside the tumour while preserving healthy tissues, stimuli-responsive drug carriers are designed to react to these signals. The somewhat acidic environment of breast cancer tumours, for instance, may be used as a trigger to release drugs [57]. The acidic environment in the tumour tissue causes nanoparticles or carriers to release the therapeutic payload as they enter, increasing drug exposure to cancer cells and reducing adverse effects in surrounding tissues [58]. Improved medication bioavailability at the target location and less systemic toxicity are two benefits of this strategy. It has enormous potential to improve therapeutic effectiveness in the treatment of breast cancer.

4. Types of targeted drug delivery systems in breast cancer:

Numerous innovative targeted drug delivery systems have emerged as a result of the search for more accurate and efficient cancer treatments. These cutting-edge methods aim to improve delivery to cancerous cells while preserving healthy tissues. This section examines the wide range of cancer targeted delivery platforms, including polymer-based carriers, liposomal formulations, ADCs, and nanoparticle-based systems (Fig. 4). To improve the therapeutic effect of anti-cancer medications, each of these systems makes use of unique technologies and processes. By thoroughly analyzing these methods, we want to draw attention to the developing tactics that have potential in the fight against cancer, namely breast cancer [59].

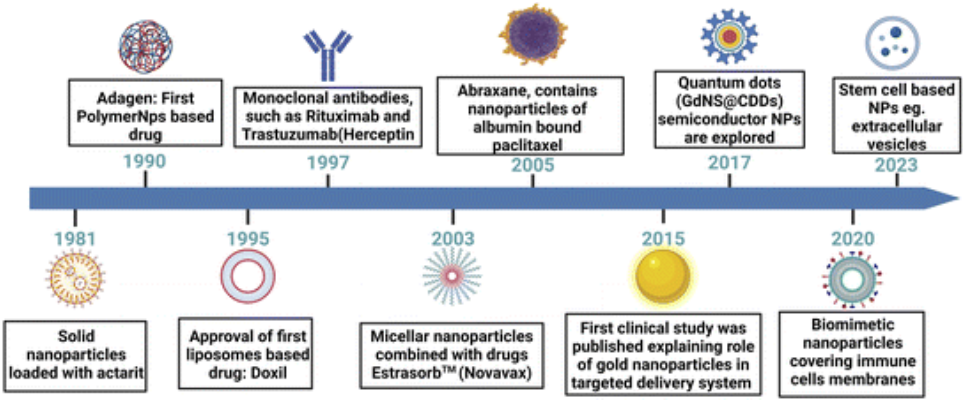

Figure 4: A schematic presentation of a chronological journey through the evolution of drug delivery systems.

4.1. Nanoparticle-based drug delivery systems:

There are many benefits of using nanoparticles in targeted medicine delivery for cancer treatment. These include improved solubility of hydrophobic medications, regulated release patterns that maximise therapeutic results, and precise targeting achieved by functionalization with ligands [59]. Additionally, nanoparticles are biocompatible, preserve encapsulated medications, and may pass through biological barriers to deliver pharmaceuticals to certain regions more effectively [60]. Additionally, its versatility enables customised methods for therapy monitoring and diagnosis. High cellular absorption rates also guarantee effective drug delivery to target cells, which together improve the effectiveness and adaptability of drug delivery systems based on nanoparticles in the treatment of cancer. [61]. Recent innovations in delivery platforms mediated by nanoparticles have shown revolutionary breakthroughs in the treatment of breast cancer. For example, scientists have used paclitaxel-loaded albumin nanoparticles (Abraxane®) to their advantage. 62 By increasing paclitaxel's solubility, this formulation facilitates its transport to breast cancer cells, enabling lower dosages and fewer adverse effects. 63 More recently, a study with patients who had breast cancer showed that Abraxane® was more effective than traditional paclitaxel formulations[64,65].

The positive-charged Au+ ions found in gold nanoparticles (GNPs) are essential to their ability to act as carriers that selectively target tumours. GNPs use electrostatic interactions to draw in negatively charged biomolecules. In parallel, linker molecules containing thiol or nitrogen (N) groups are used to modify GNPs with organic or polymeric ligands. There are many different physiological impacts that arise from this link[66,67]. For example, in a work by Li and colleagues, a novel method was used to produce calcium phosphate (CaP)-based yolk-shell nanoparticles. The yolk of these nanoparticles was a detachable gold nanorod. Interestingly, these nanoparticles demonstrated remarkable loading efficiency, encapsulating up to 100% of doxorubicin (DOX) molecules. Additionally, when subjected to either acidic circumstances or NIR laser stimulation, they were able to aggregate inside tumours and release DOX because to their dual-response mechanism, which is sensitive to both pH and NIR light [68].

Since its crystalline core has a special superparamagnetic property, magnetic nanoparticles (MNPs) have also been studied. When subjected to an external polarised magnetic field, this characteristic enables them to change their microwave magnetic response without affecting the surroundings. They are thus crucial contrast agents in the fields of tumour imaging and cancer diagnostics. Furthermore, MNPs are positioned as potential vehicles for targeted drug administration in research due to their selectivity in targeting tumour tissues utilising particular antigens found on tumour cell receptors [69]. To improve their stability and circulation, Zou and colleagues synthesized mesoporous MNPs containing DOX encapsulated and functionalised with chitosan [70]. When exposed to alternating current (AC) electromagnetic fields, these mesoporous MNPs showed a significant DOX encapsulation and were effective in detecting breast cancer. Additionally, in a different study by Semkina et al., anti-vascular endothelial growth factor (VEGF) monoclonal antibodies were functionalised with polyethylene-glycolized magnetic nanoparticles (PEG-MNPs) in order to transport DOX. This method made it easier for these PEG-MNPs to accumulate at the tumour, and the magnetic core produced strong signals that could be seen using real-time magnetic resonance imaging (MRI) monitoring. 71 To improve photothermal treatment (PTT) for breast cancer, Hu et al. have created hollow copper sulphide nanoparticles modified with hyaluronic acid that encapsulate diethyldithiocarbamate (DDTC) in combination with losartan. This method inhibits the formation of metastatic tumours by improving medication accumulation, enhancing anti-tumor effects, inducing efficient immunogenic cell death (ICD), and remodelling the tumour microenvironment [72].

4.2. Liposomal formulations for targeted delivery:

With several benefits, liposomes are a flexible targeted medication delivery method. They improve drug stability, protect medications from deterioration, and reduce adverse effects by limiting exposure to healthy tissues [73]. Customised adjustments allow for accurate administration to certain cells or tissues, increasing the precision and effectiveness of therapy [74]. Furthermore, liposomes are biocompatible and biodegradable, which guarantees their safety for drug delivery applications, and they provide customisable properties like composition and size [75]. Liposomes have significant potential to improve the efficacy and safety of medication therapies in a variety of medical domains by using these characteristics [76]. Liposomes are spherical structures made of lipid bilayers that are both biodegradable and biocompatible. These lipid bilayers provide a special setting that protects hydrophobic medications inside the lipid membrane while permitting the encapsulation of hydrophilic medications within the aqueous core [30]. In order to provide accurate targeted distribution in breast cancer treatment, liposomal formulations have undergone substantial refinement. Targeting overexpressed receptors on cancer cells using liposomes coupled with monoclonal antibodies is one recent advancement. Interestingly, liposomal doxorubicin and the anti-HER2 antibody trastuzumab (Herceptin®) improve drug delivery to HER2-positive breast cancer cells, leading to better treatment results [77]. Liang and colleagues78 used siRNA to breast cancer cells that overexpressed heat-shock protein-gp96 using cationic liposomes coated with peptide-p37 (CDO14). To improve liposome targeting, the p37 peptide—which inhibits gp96, a new tumors therapeutic target—was added. In comparison to unmodified liposomes, their investigations

demonstrated a much stronger tumors inhibition effectiveness and a remarkable gene silencing efficacy using p37-CDO14. Another research team used thermosensitive liposomes with parthenolide, an anti-cancer natural plant chemical, and photosensitizer cyanine dye as part of a combinatorial treatment for TNBC [78]. Indocyanine green produced heat when exposed to near-infrared light, which changed the structure of the thermosensitive liposomes and caused the medication to be released. When compared to paclitaxel, this customized liposomal formulation demonstrated a 2.08-fold improvement in tumors suppression. It is important to remember, nevertheless, that these results need to be supported by more research and in vivo confirmation [79]. In order to improve the therapy of breast cancer, Jain et al. were the first to synthesize pH-responsive liposomes that were loaded with DTX and surface-functionalized with VEGF antibodies. When compared to free DTX, their analysis showed increased cellular absorption, an improved drug release profile in acidic conditions, and a longer pharmacokinetic half-life [80]. with a related work, Cao et al. used pH-sensitive liposomes coated with macrophage membranes to administer the potent anticancer medication emtansine utilising a biomimetic drug delivery technique. This method improves liposomes' ability to target certain metastatic sites. Their results support the significant growth inhibition brought about by the major increase in the specificity of lung metastasis targeting in breast cancer. There is a lot of promise for improving breast cancer treatment with these creative approaches [81].

4.3. Antibody–drug conjugates (ADCs):

By precisely targeting cancer cells, antibody–drug conjugates in targeted medication delivery reduce systemic toxicity and off-target consequences. They can get past biological barriers and increase the effectiveness of therapy by concentrating cytotoxic medicines at tumour locations. ADCs may be customised for certain tumour types for customised treatment and used in conjunction with other medicines for synergistic benefits. All things considered, ADCs provide a viable way to raise the effectiveness and security of cancer therapies [82]. ADCs are a powerful new class of targeted treatments for breast cancer. ADCs are a new type of biopharmaceuticals made up of mAbs that have been chemically connected to small-molecule medications via bioactive connectors. Two crucial factors influencing the effectiveness of ADCs have emerged throughout their development: the careful construction of the linker that joins the monoclonal antibody to the therapeutic payload and the calculated conjugation of a strong chemotherapeutic agent to the monoclonal antibody [83].

In 2000, Gemtuzumab ozogamicin (Mylotrag®), the first of its type, was approved as the first ADC. This ADC contains gemtuzumab, which is conjugated by non-specific lysine attachment to N-acetyl gamma calicheamicin dimethyl hydrazide. Its linker was notable for having a hydrazone bond that was intended to break down in the target cells' acidic intracellular environment, releasing the anti-tumor antibiotic calicheamicin. Nevertheless, the linker of this ADC was shown to be susceptible to circulatory instability, which led to the early release of cytotoxic calicheamicin payloads. Due to the unanticipated harmful consequences of this release, Pfizer voluntarily removed Gemtuzumab ozogamicin off the market in 2010 [84].

The FDA approved sacituzumab govitecan-hziy (Trodelvy®), an ADC that targets breast cancer that expresses Trop-2, after it showed exceptional clinical performance [62]. Trodelvy®'s efficacy in treating refractory metastatic triple-negative breast cancer has been further validated by recent clinical trials [64,85] underscoring the critical role that ADCs play in the treatment of breast cancer today.

4.4. Polymer-based drug carriers:

Because of their many benefits, polymeric nanoparticles are preferred in targeted medication delivery. They provide prolonged release patterns and regulated medication release, reducing the frequency of doses. Functionalisation improves treatment results by enabling precision targeting and lowering off-target effects [86]. Furthermore, by enhancing drug accumulation at target areas and decreasing systemic toxicity, polymeric nanoparticles enhance pharmacokinetics [87]. For a variety of uses, they may encapsulate a large variety of medications, such as proteins, genes, hydrophilic and hydrophobic chemicals, and imaging agents [88]. Furthermore, they show promise for clinical translation because to their

biocompatibility, scalability, repeatability, and simplicity of functionalisation. These characteristics demonstrate polymeric nanoparticles' potential as efficient drug delivery vehicles for a range of therapeutic uses [89].

Personalised approaches to treating breast cancer are being propelled by advancements in polymer-based medicinal carriers. A new development is polymeric micelles, which are intended to provide better bioavailability and controlled medication release. In order to increase the anticancer effectiveness of axitinib and paclitaxel against breast cancer, recent studies have concentrated on dual pH-responsive micelles for co-delivery [90].

Peng et al. conjugated Herceptin with PCL–PEG to create designed worm-like nanocrystal micelles for the targeted therapy of breast cancer that overexpresses HER2. Targeting HER2+ positive cells specifically, these micelles, which included paclitaxel (PTX) and Herceptin, demonstrated exceptional stability in the circulation and tumour microenvironment (TME) [91]. Meanwhile, by adding pendant benzyl carboxylate groups to the PCL segment of PEO–PCL, Garg et al. created traceable polymeric micelles known as PEO–poly(α-benzyl carboxylate-ε-caprolactone) (PEO–PBCL). They also included the NIR probe Cy5.5 into these micelles' core-forming block. Consequently, these altered micelles demonstrated enhanced stability, better accumulation at tumour sites, and real-time disease progression monitoring in in situ breast cancer mouse models. These developments have great potential for accurate and successful treatment of breast cancer [92]. In order to provide an adjuvant, Aleanizy and colleagues developed a delivery method that used a PAMAM dendrimer in conjunction with trastuzumab. Comparing these dendrimers to the stand-alone medications, their results demonstrated improved cellular uptake, cytotoxicity, and selectivity. These results imply that these dendrimer-based systems have a great deal of potential as platforms for targeted medication delivery in the treatment of breast cancer [93].

4.5. Other emerging targeted delivery approaches:

Several novel targeted delivery strategies are being developed in the treatment of breast cancer, as shown in Fig. 5, in addition to nanoparticle-based systems, liposomal formulations, ADCs, and polymer-based carriers. These methods improve the accuracy and effectiveness of treatments by using cutting-edge technology and biological understanding. Here are a few prominent new approaches:

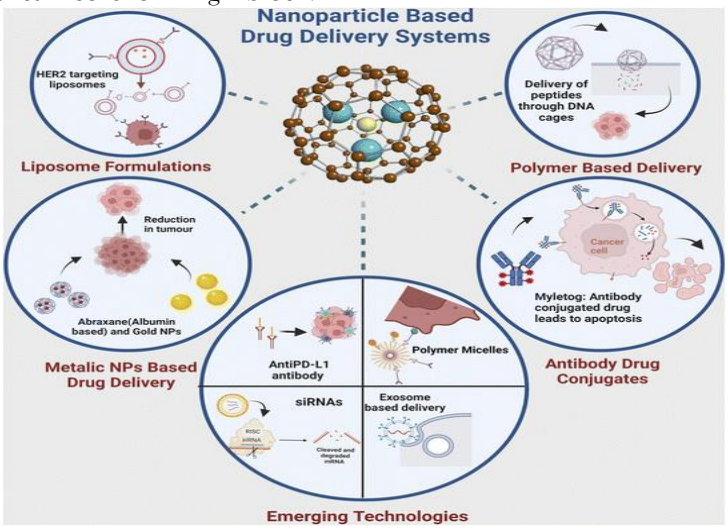

Figure 5: Emerging targeted drug delivery systems for precision breast cancer therapy. Nanoparticles, liposomes, antibody–drug conjugates, polymeric micelles, and exosomes can be engineered to selectively deliver chemotherapeutic agents, RNA therapeutics, and immunotherapy to breast tumors. Surface functionalization with tumor-targeting ligands enhances selective uptake. Stimuli-responsive and multifunctional designs allow controlled drug release and real-time monitoring. These innovative

technologies aim to improve treatment efficacy and safety through targeted delivery to cancer cells while sparing healthy tissues.

4.5.1. Exosome-based drug delivery:

Cells release tiny vesicles called exosomes, which are essential for intercellular communication [94]. The utilisation of exosomes as natural medication delivery vehicles has been investigated recently. Because of their lipid bilayer structure that prevents cargo from degrading and their surface proteins that allow for exact cell targeting, exosomes have benefits in cancer treatment for targeted medication delivery [95]. While extended circulation guarantees sustained drug release and enhanced bioavailability, their function in intercellular communication helps to modulate cellular responses. Because of their low immunogenicity and capacity to penetrate cellular barriers, exosomes provide a prospective avenue for improving cancer therapy effectiveness and safety [96]. This method seems promising for using the body's communication system to distribute drugs. By creating an exosome from MSCs loaded with DOX, Bagheri et al. were able to achieve a 35% encapsulation efficiency [97]. MUC1 aptamer functionalisation enhanced the targeting of cancer cells. The effectiveness of MUC1apt–MExo–DOX in cancer treatment was shown in a C26 carcinoma mouse model, where it drastically decreased the volume of cancer and guaranteed 100% survival after 30 days [98, 99]. In order to deliver anti-cancer drugs, Yong et al. developed an inorganic NP-exosome hybrid structure in which DOX was loaded into mesoporous silicon NPs (DOX–MPS) and administered to cancer cells. The DOX-MPSs formed DOX-MPS/exosome core/shell structures after entering H22 or Bel7402 cells by endocytosis. The therapeutic potential of these hybrids was confirmed by their anti-cancer activities in B16–F10 lung metastasis mice and H22 tumor-bearing mice [100].

4.5.2. Peptide-targeted therapies.

Short sequences of amino acids called peptides are made to attach to cancer cell surface receptors. Targeted medicines based on peptides are becoming more popular for treating breast cancer. These peptides may be used as components of ADCs or as homing devices for drug-loaded nanoparticles, guaranteeing accurate drug delivery to tumour cells while avoiding healthy tissues[101, 102]. Personalised therapy based on the molecular features of the breast tumour might be possible with this approach. [74]. PEG-conjugated peptides DH6 (YLFFVFER) and RDH6 (REFVFFLY) were created by Du et al. and showed high metabolic stability and precise targeting of HER2-positive tumours [103]. Additionally, Stefanick et al. examined the cellular absorption of HER2-targeting peptides HERP5, HRAP, KAAYSL, and AHNP; KAAYSL showed the maximum tumour uptake [104]. To deliver salinomycin precisely to breast cancer cells, Hailing et al. created nanoparticles made of D-α-tocopheryl polyethylene glycol 1000 succinate and GE11-modified polylactic-co-glycolic acid (PLGA). Their results showed that these nanoparticles greatly increased the effectiveness of treatment, especially in instances of breast cancer when EGFR overexpression was present. [105,106].

4.5.3. RNA-based therapeutics:

Treatment for breast cancer is changing as a result of developments in RNA-based therapies, such as messenger RNA (mRNA) and small interfering RNA (siRNA). These compounds may be engineered to specifically target genes or proteins implicated in the development and spread of cancer. High-precision RNA therapies may be delivered to breast cancer cells using nanoparticle-based carriers, providing a possible means of protein expression modification or gene silencing. [107].

In order to target the neuropilin (NPR) receptors on breast cancer (BC) tumour cells, Yan et al. created nanosized liposomes conjugated with tLyp-1 peptide. In vitro and in vivo, this nanoformulation inhibited the TGF-β1/Smad pathway and caused post-transcriptional silencing of Slug when loaded with a miR-203 mimic [108]. Using poly(β-amino ester) and poly(D,L-lactide-co-glycolide) polymers, a targeted delivery system was created to deliver epirubicin and antimir-21 to cancer cells. MUC1 aptamer alteration decreased vitality without influencing MUC1-negative CHO cells by facilitating selective absorption by MCF7 and C26 cells. Compared to epirubicin alone, this nanocomplex demonstrated improved safety and effectiveness in slowing tumour development in animal models [109]. In order to transfer siRNAs to breast cancer cell lines, Nayak et al. created cationic

liposomes using dicta decyl amido glycyl spermidine (DOGS) and DOPE. They were able to achieve effective delivery and precise localisation close to the nucleus. In addition to efficiently delivering plasminogen activator inhibitor type I-specific siRNA to MDA MB 231 cells, these liposomes demonstrated little cytotoxicity and promoted high absorption of cyclin D1-specific siRNA in MCF-7 cells [110].

4.5.4. Immune checkpoint inhibitor delivery:

Immunotherapy is a potential therapeutic option for aggressive subtypes of breast cancer. Research is being done on the targeted administration of immune checkpoint inhibitors, including anti-PD-L1 antibodies, to the tumour microenvironment. By reducing systemic adverse effects and boosting the anti-tumor immune response, this strategy may increase the effectiveness of immunotherapy for breast cancer [30].
Bakhos et al. delivered the STING agonist 2′3′-cGAMP using virus-like particles (VLPs) [111]. Packaged inside enveloped virus particles, 2′3′-cGAMP, a natural mammalian STING agonist, instantly activates STING in DCs upon fusion [112,113]. HIV-1 structural protein and vesicular stomatitis virus envelope glycoprotein make up the synthetic VLPs that encapsulate cGAMP. According to this research, cGAMP-VLPs were around fifty times more effective in delivering cGAMP into cells than traditional liposomes [114].

5. Targeted drug delivery at preclinical and clinical level:

The path from ideation to clinical implementation in targeted medication delivery for breast cancer entails a thorough investigation that includes both rigorous clinical trials involving patients with breast cancer and preclinical investigations in laboratory models. This section gives a thorough summary of preclinical research and clinical trials, shedding light on the advancements, difficulties, and noteworthy results in targeted medication delivery for breast cancer.

5.1. Overview of preclinical studies on targeted drug delivery in breast cancer models:

The fundamental cornerstone for evaluating the safety and effectiveness of delivery methods is preclinical research. To reproduce and understand the behaviour of drug carriers and therapeutic agents within the complex tumour microenvironment, these investigations primarily use laboratory models, such as cell cultures and animal models [29]. There are many uses for preclinical research. These studies are used by researchers to explore important topics, such as the pharmacokinetics, biodistribution, and toxicity profiles of drug carriers. Additionally, they carefully examine these systems' ability to accurately and successfully target breast cancer cells while minimising harmful effects on healthy tissues. To maximise therapeutic effectiveness, preclinical research often entails adjusting carrier characteristics, such as particle size, surface chemistry, drug release kinetics, and the incorporation of targeting moieties [58]. A wide range of tailored medication delivery strategies have shown promise in recent preclinical research. Increased drug accumulation in breast tumours, increased anti-tumor activity, and reduced systemic adverse effects have all been shown by these studies [115]. These results, which have their roots in scientific rigour, are crucial first steps that open the door for further clinical translation.

5.2. Clinical trials and outcomes of targeted drug delivery systems in breast cancer patients:

When assessing targeted medication delivery methods for the treatment of breast cancer, clinical studies are essential. These studies, which are carefully planned to assess the safety, effectiveness, and overall clinical advantages of these novel therapy paradigms, must include patients with breast cancer [55].
A wide range of targeted drug delivery methods, including nanoparticle-based formulations, ADCs, and stimuli-responsive carriers, have been tested in recent clinical studies for various breast cancer subtypes. Typically, these studies target certain patient groups, including those with HER2-positive or triple-negative breast cancer, and carefully examine objectives that include tumour response rates, progression-free survival, and the overall effect on disease quality of life [116].
In addition to approving a number of targeted drug delivery systems for the treatment of breast cancer, promising results from recent clinical studies have given patients new hope. Notable instances include the ASCENT study, which highlighted the advantages of sacituzumab govitecan in metastatic triple-negative breast cancer, and the HER2CLIMB trial, which

showed the effectiveness of tucatinib in HER2-positive breast cancer.[77,117]. However, there are still issues that need to be investigated and improved, such patient selection standards, the best ways to dose patients, and the development of resistance mechanisms [118].

6. Challenges and future directions:

A concentrated effort is required to overcome the significant obstacles in the pursuit of optimal targeted medication delivery in breast cancer. This section examines these issues from a scientific perspective and considers possible future paths informed by research results and empirical data.

6.1. Overcoming biological barriers in targeted drug delivery to breast cancer:

The complex tumors microenvironment presents significant obstacles to accurate medication administration since it is a dynamic and diverse terrain. It is a constant struggle to get the best possible medication penetration, circulation stability, and specificity [119]. For the field to advance, strategies to overcome these obstacles are essential. By using an immunoliposome-based delivery system to administer a chemotherapeutic medication and the microRNA linked to its drug resistance, Fig. 6 shows a viable strategy for overcoming drug resistance that targets cancer cells while preserving healthy tissues.

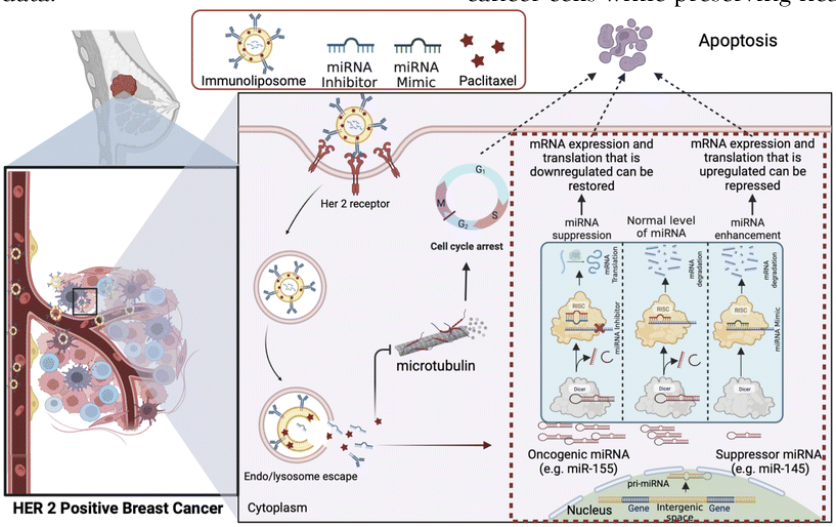

Figure 6: Next-generation liposomes: immunoliposomes, armed with anti-HER2 antibodies, encapsulate conventional chemotherapeutic drugs and specific miRNAs linked to drug resistance mechanisms. This precise dual-targeted approach ensures the selective delivery of therapeutic cargo to cancer cells, sensitizing them to chemotherapy through miRNA modulation via miRNA inhibitors or mimics. The combined delivery of miRNAs and drugs results in a potent synergistic effect, allowing for lower drug concentrations while inducing apoptosis in cancer cells, potentially revolutionizing the treatment of HER2-positive breast cancer by overcoming drug resistance and minimizing adverse effects.

Recent advances in the engineering of nanoparticles provide promising opportunities. For example, Zheng and colleagues (2020) have developed pH-responsive nanoparticles that can effectively manoeuvre through the complexities of the tumour microenvironment, enabling regulated drug release and greatly enhancing treatment effectiveness [119].

6.2. Biodegradation and clearance of nanocarriers:

Assessing the safety profile and possible long-term consequences of drug carriers in the field of nanomedicines requires a thorough knowledge of their post-delivery biodegradation and clearance [120]. The release of encapsulated medications and metabolites inside the body is influenced by the critical breakdown of nanocarriers [121]. Clearance pathways—whether hepatic metabolism, renal excretion, or other pathways—are also essential for assessing medication pharmacokinetics and systemic effect [122].

The biodegradation and clearance mechanisms of many nanocarrier systems used in drug delivery have been clarified by recent studies. For example, research has shown that polymeric nanoparticles, such PLGA (polylactic-co-glycolic acid)) carriers, may biodegrade into innocuous metabolites that are ultimately eliminated from the body [123]. Likewise, studies on lipid-based nanocarriers, such as liposomes, have shown degradation mechanisms that allow for the safe removal of the loaded medication as well as the carrier [124].

Furthermore, research into hybrid nanocarriers—which blend various components including metals and polymers—has shed light on their clearing processes and biodegradation patterns [120]. Studies on silica-based nanocarriers have shown their promise for safe removal from the body and regulated breakdown [125]. Furthermore, using biodegradable dendrimers as nanocarriers has shown promise in promoting efficient drug release while guaranteeing biocompatibility and ultimate clearance [126].

6.3. Immunological considerations and strategies for improved efficacy:

When it comes to targeted medicine delivery to breast cancer, immunological subtleties are crucial. Treatment results are greatly impacted by the interaction of therapeutic drugs, drug transporters, and the host immune system [127]. There is a lot of promise in developing strategies to control and manipulate these interactions.

The significance of including immunomodulatory drugs in targeted drug delivery scenarios is highlighted by recent study by Gu et al. (2022). Their research on the co-administration of immunostimulatory drugs with chemotherapy has produced significant findings, leading to improved tumour shrinkage and a strong immune response in models of breast cancer [128].

6.4. Translational challenges:

Although nanomedicines have great promise for targeted drug delivery in breast cancer treatment, there are still several obstacles in the way of their clinical translation [129]. Concerns about possible toxicities from the nanocarriers or the development of a protein corona in bodily fluids are raised by the intricacy of multicomponent nanosystems, which makes them vulnerable to instability, aggregation, and uncontrolled drug release [130]. It is difficult to increase output while preserving the intended physicochemical characteristics and medicinal effectiveness. These nanomedicines face physiological obstacles like the blood–brain barrier in metastatic illness and biological barriers like the high interstitial fluid pressure and thick extracellular matrix in the tumour microenvironment when used in vivo [131]. The biodistribution, cellular absorption, and toxicity profiles of nanoparticles are significantly impacted by the formation of a protein corona by the adsorption of plasma proteins onto their surfaces. The constraints of traditional animal models make preclinical evaluation more difficult, which calls for the creation of more representative platforms like organoids [132]. Moreover, a major barrier to the effective clinical translation of complicated nanomedicines is the lack of standardised regulatory standards for assessing their efficacy, safety, and quality. To overcome these complex obstacles and forward the translation of targeted drug delivery systems for breast cancer treatment, interdisciplinary collaboration is crucial [133,134].

6.5. Regulatory aspects and commercialization prospects:

Important turning points in the development of targeted drug delivery systems for breast cancer include navigating the regulatory environment and achieving commercialization opportunities. Regulatory approvals are contingent upon strong preclinical and clinical data supporting effectiveness and safety [135]. Scalability, cost-effectiveness, and market accessibility must all be taken into account for commercial success.

Targeted drug delivery has enormous promise for treating breast cancer, as shown by recent commercial successes and regulatory approvals. The approval of sacituzumab govitecan (SG) for triple-negative breast cancer and trastuzumab emtansine (T-DM1) for HER2-positive breast cancer are noteworthy examples [55, 77]. These turning points show the way ahead and show how important it is to keep funding research and development.

7. Conclusion:

As we approach to the end of this thorough investigation into targeted medication delivery in breast cancer, it is clear that this area has advanced

remarkably and has great potential for better patient outcomes. We highlight the revolutionary potential of targeted drug delivery in the treatment of breast cancer in this conclusion, which summarises important discoveries and developments. We also go over the encouraging viewpoints that set the groundwork for this dynamic field's future.

7.1. Summary of key findings and advancements in targeted drug delivery for breast cancer:
Recent years have seen significant progress in targeted drug delivery strategies for breast cancer, propelled by innovative research and technology. Noteworthy findings and advancements include:

7.1.1. Precision and specificity: By reducing off-target effects, targeted medication delivery systems have significantly improved the therapeutic agents' specificity and accuracy. Trastuzumab emtansine (T-DM1) for HER2-positive breast cancer and SG for TNBC are noteworthy examples [55,77].

7.1.2. Overcoming barriers: Novel approaches to getting beyond biological barriers in the tumour microenvironment have surfaced, including immunomodulatory drugs and pH-responsive nanoparticles. Drug penetration and treatment results have improved as a result of these developments [128,136].

7.1.3. Immunomodulation: It has been shown that incorporating immunostimulatory substances into targeted medication delivery systems may produce strong immune responses. As shown by the combination of immunotherapies with chemotherapy, this has created new opportunities for synergistic therapeutic methods [137].

7.1.4. Commercial success: The viability and economic promise of customised breast cancer treatments have been reaffirmed by regulatory approvals and the successful marketing of targeted drug delivery systems, such as T-DM1 and SG [55, 77].

7.1.5. Patient-centric care: Targeted drug delivery's development is consistent with the personalised medicine paradigm, offering progressively customised therapies based on the molecular subtypes, illness stages, and patient profiles [138].

7.2. Perspectives on the future of targeted drug delivery in breast cancer treatment:
Targeted medication delivery in the treatment of breast cancer has a bright future ahead of it. Attention should be paid to many important viewpoints and directions:

7.2.1. Precision oncology: It is anticipated that more accurate and customised targeted medication delivery systems would be created by combining genomic and proteomic data with cutting-edge machine learning algorithms [139]. Gene expression profiling has the ability to inform therapy choices and improve results, as seen by recent projects like the TAILORx study [140].

7.2.2. Combination therapies: There is a lot of promise in the combination of targeted medication delivery and new immunotherapies. In order to facilitate the development of more potent combination treatments, ongoing research initiatives seek to clarify the complex interactions between the immune system and the tumour microenvironment [137].

7.2.3. Biomarker discovery: Research is still focused on finding biomarkers, which makes it possible to find new molecular targets and create companion diagnostics [141]. Promising biomarkers such as PD-L1 and TILs (Tumor-Infiltrating Lymphocytes) have been identified in recent research as indications of immunotherapy response [142].

7.2.4. Regulatory harmonization: For novel targeted drug delivery systems to be quickly implemented in clinical settings, regulatory harmonisation across regions is essential [143]. A positive step has been taken recently by international initiatives including the World Health Organization's endeavour to harmonise worldwide regulatory standards [144]. In summary, tailored medication administration for breast cancer has progressed from a theoretical notion to a practical application that has the potential to completely transform patient care. There is a great deal of promise in recent developments, such as

precision medicines, novel drug carriers, and immunomodulatory techniques. With an increasing focus on combining interdisciplinary research and a patient-centric approach, the future offers great opportunities for even more individualised, efficient, and accessible breast cancer therapies.

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Muhammad Junaid Ahmed: literature review, data analysis, writing – original draft preparation. Doctor Ahmad Subhan: writing – reviewing and editing. Doctor Nazam Naveed and Doctor Ghulam Mustafa (corresponding author): conceptualization, supervision, writing – reviewing and editing.

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There are no conflicts to declare.

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