Review

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Abstract: Breast cancer (BC) is one of the most common types of cancer in women. Triple-negative breast cancer (TNBC), characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), exhibits a highly aggressive phenotype with increased metastasis and resistance to conventional treatments. Nanocarrier technology is consistently employed to overcome limitations associated with traditional breast cancer therapy. The targeted drug delivery approach using nanocarriers enhances bioavailability, prolongs circulation, and facilitates effective drug accumulation at the tumor site through active or passive targeting. Currently, the FDA has approved a few nanocarrier systems, and numerous nano formulations are undergoing preclinical and clinical development for breast cancer targeting. Common nanocarrier types include polymeric micelles, microemulsions, magnetic microemulsions, liposomes, dendrimers, carbon nanotubes, and magnetic nanoparticles (NPs). This review extensively explores the targeting potential of nanocarriers in breast cancer. This study will provide a concise summary of current advances in treatment of breast cancer and diagnostics.

Keywords: Breast cancer; Nanocarriers; Tumor location; Diagnostics

1. Introduction

Breast cancer stands as the most prevalent form of cancer among women. Early-stage, non-metastatic cases of this cancer are treatable in around 70 to 80 percent of individuals[1]. Breast cancer is a term used to describe malignancies that develop from breast tissue, most frequently from the lobules that provide the milk ducts with milk or the inner lining of the milk ducts.2 Males tend to have worse results due to delays in detection, although breast cancer affects women around 100 times more frequently than it does men. Cancer cells have comparable (but not identical) DNA and RNA to the cells of the organism from whence they arose. This is why they are seldom picked up by the immune system, especially if it is already compromised.3[3] Worldwide, there is a significant disparity in breast cancer survival rates, with industrialized nations having an estimated 5-year survival rate of 80% and underdeveloped nations having a survival rate of fewer than 40%. Resource and infrastructural shortages in developing nations make it difficult to achieve the goal of improving breast cancer outcomes through early detection, diagnosis, and treatment.2[2] The regulation of breast

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cancer and the spread of metastases are controlled by a number of mechanisms. Breast cancer is categorized into three primary subtypes based on molecular markers, namely human epidermal growth factor 2 (ERBB2, formerly known as HER2), estrogen receptor (ER), and progesterone receptor (PR). These markers help classify tumors as hormone receptor positive/ERBB2 negative (accounting for approximately 70% of patients), ERBB2 positive (15%-20%), and triple-negative (15%), referring to tumors that lack expression of all three standard molecular markers. Understanding the biological activity of ERs (estrogen receptors), PRs (progesterone receptors), and HER-2 (human epidermal growth factor receptor 2) for various subtypes of breast cancer has advanced.[4,5] The most often employed and successful treatment for breast cancer is chemotherapy. Low selective site-specificity, and the resulting toxic insult to normal, healthy cells, is one of the main downsides. Consistently, the nanocarriers system is used to reduce the many drawbacks of the standard care for breast cancer.[6]

To increase the therapeutic effectiveness of anticancer medications, several nanocarriers have been developed, including liposomes, polymeric micelles, quantum dots, nanoparticles, and dendrimers.[7] According to studies, the utilization of nanocarriers for combinational delivery has shown encouraging outcomes in addressing breast cancer.[8] Traditional treatment methods pose risks to non-targeted areas, causing harm to normal cells. Consequently, there is a growing inclination towards developing chemotherapeutic approaches that inflict minimal or no damage to patients while actively or passively targeting malignant cells. Employing nanoparticles holds promise in delivering customized drugs directly to tumor cells, resulting in an increased concentration of medication within cancer cells through active or passive targeting strategies.[9]

2. Human Breast cancer and its stages

According to a report from breast cancer.org, the breast cancer's stage is determined by the size, shape, and depth of the tumor cells' invasion into the breast tissues. Stage 0 refers to non- invasive tumors, whereas Stage 1 defines invasive breast cancer with the possibility of microscopic penetration. Stage 2, Tumors may range in size from less than 2 cm to more than 5 cm. Stage 3 describes inflammatory breast cancer, which includes the spread of the tumor to 10 or more axillary lymph nodes and involvement of the lymph nodes above and below the clavicle, and stage 4 describes the lymph nodes above and below the clavicle. The Figure 1. below shows all the stages of breast cancer[10]

BRCA gene germline mutations have been shown to be responsible for 5–10% of breast cancer cases.[11] Around 70% of occurrences of breast cancer are categorized as sporadic. There are a variety of high-, moderate-, and low-penetrance susceptibility genes that have been linked to familial breast cancer, which affects roughly 30% of patients and is frequently observed in families with a high incidence of breast cancer.[12]

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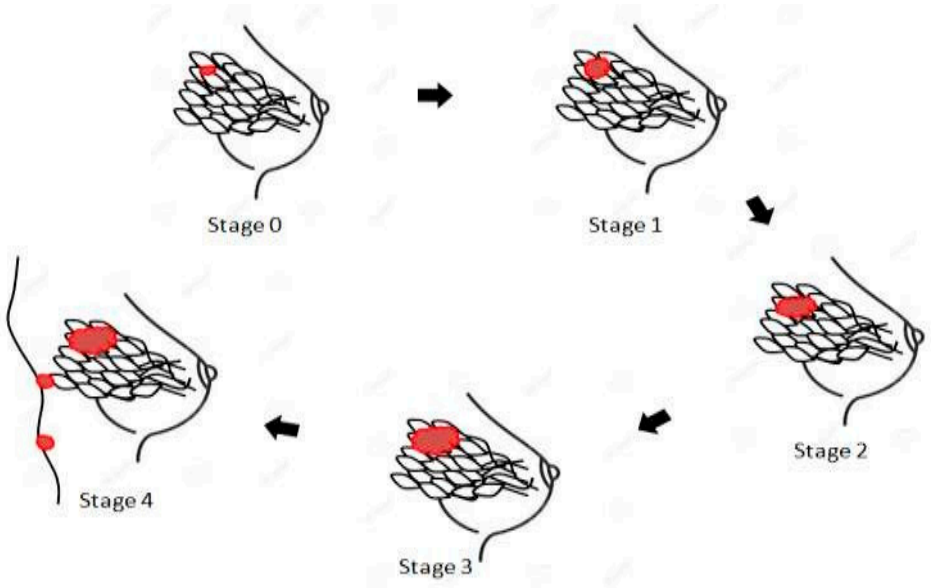

Figure 1. The stages of breast cancer.

The Tumor-Node-Metastasis (TNM) system, which was introduced by Pierre Denoix in 1942, was designed to classify cancer based on important visual features of malignant tumors that were thought to influence the prognosis of the disease. This system took into account factors such as the size of the primary tumor (T), involvement of regional lymph nodes (N), and the presence of distant metastases (M). In 1958, the International Union Against Cancer (UICC) introduced a clinical breast cancer classification based on TNM, and in 1977, the American Joint Committee on Cancer (AJCC) adopted this system into their initial cancer staging manual. Over the years, updates have been made to incorporate advancements in diagnosis and treatment. Notably, in the 1987 revision, discrepancies between the AJCC and UICC versions of the TNM system were resolved. For example, data from the National Cancer Database (NCDB) shows that the percentage of US patients initially diagnosed as Stage 0 or Stage I increased from 42.5% in 1985 to 56.2% in 1995, while the percentage of patients diagnosed as Stage III or Stage IV decreased from 18.3% to 11.6% during the same period.[13] Recent advancements in clinical research are reflected in adjustments to the new TNM/AJCC classification. The axillary node status additions are the most significant. The terms "micrometastasis" and "isolated tumor cells" have been modified, as have the various sentinel lymph node biopsy detection techniques.[14]

3. Recent advancements in detection of breast cancer

Analyzing the factors that have influenced the changes in the occurrence and fatality rates of breast cancer over recent decades provides crucial insights into the role of breast screening, the widespread utilization of adjuvant medications, and the evolution of risk factors.[17] Detecting breast cancer at an early stage is associated with improved outcomes for individuals undergoing treatment, as small, non-metastatic (early) diseases can be effectively managed, potentially leading to a 5-year survival rate increase. Employing breast cancer screening measures is crucial for enhancing patient outcomes. Additionally, early detection and treatment of breast cancer contribute to an improved quality of life for women by enabling the use of less invasive surgical interventions.[18]

Following a diagnosis of invasive breast cancer, the primary responsibility is to discern which patients should undergo chemotherapy and which should not.

After selecting adjuvant therapy, the subsequent challenge lies in identifying the most effective treatment or combination of therapies tailored to an individual patient. Prognostic biomarkers play a crucial role in resolving the initial challenge, while predictive biomarkers contribute to addressing the second. Key molecular markers such as ER, PR, HER2, and the Mib1/Ki-67 proliferation index are highly significant in the context of breast cancer (BC) and undergo thorough validation in the routine

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care of both primary and recurrent, as well as metastatic BC patients..[19] Many sensitivity-enhancement procedures have been applied to date with a diverse range of nanomaterials and nanoparticles (NPs) to increase the limit and sensitivity of analyte detection in the development of novel aptasensors.[20] Cancer patients' plasma contains tumor-derived circulating cell-free DNA (cfDNA). Assays for identifying common cancer mutations in cfDNA are being developed for a variety of cancer types. Pretreatment breast cfDNA was found with an 80% sensitivity and 97% specificity in individuals with localized illness. Elevated amounts of cfDNA in the breast were linked to aggressive molecular tumor profiles and disease metabolic activity. Breast cfDNA levels dropped substantially with neoadjuvant treatment.21 Breast tumors can be diagnosed by analyzing numerous aspects in mammographic pictures, but one of the most prevalent is the presence of microscopic calcium deposits known as microcalcifications, which may be the sole identifiable evidence of a breast tumor in many situations.22 Yue Miao and Siyuan Tang developed a novel approach for mammography lump segmentation. The specificity and sensitivity of BRCA1/2 genetic mutation sites were all discovered in their investigation for clinically high-risk BRCA1/2 mutant carriers using a mPCR-NGS sequencing technique. As compared to standard Sanger sequence testing and target sequence testing procedures, the mPCR-NGS sequencing technology exhibited benefits such as ease of use, short time requirements, and cheap cost.23 Multiplex PCR-Nested Next-Generation Sequencing (mPCR-NGS) is a sophisticated genetic analysis method that merits in-depth exploration and contrast with the conventional Sanger sequencing approach. Several investigations have undertaken this comparison, shedding light on the advantages of mPCR-NGS. For instance, a study conducted by Li and colleagues in 2019 demonstrates the increased sensitivity and the ability to detect low-frequency mutations offered by mPCR-NGS when compared to Sanger sequencing. Additionally, research by Jones et al. in 2018 emphasizes the cost-effectiveness and the comprehensive mutation profiling capabilities of mPCR-NGS as opposed to Sanger sequencing. These studies underscore the benefits of using mPCR-NGS for genetic analysis.15,16 Biomarkers can be used to identify breast cancer in both indirect and direct ways. Proteomics and gene expression profiling approaches are anticipated to become major cancer diagnosis tools in the future. Blood-based biomarker development is the most advanced, with the potential to lead to early detection approaches in the form of proteins or RNA[24].

4. Recent developments in treatment of breast cancer

The current strategy for managing metastatic breast cancer (MBC) focuses on tailoring the patient's care to their specific breast cancer features (molecular subtype, disease burden, and prognostic indicators), as well as their clinical background (co-morbidities, prior therapies and social factors). Targeted treatment with anti-angiogenic drugs exhibits clinical action, but the trade-off between effectiveness, toxicity, and cost is still up for dispute, highlighting the unmet need for a biomarker that can predict how well a patient would respond to this type of medication. Inhibitors of poly (ADP ribose) polymerase (PARP) seem to be therapeutically effective against BRCA germline mutant breast cancer. It is yet unclear how PARP inhibitors act in various subsets of breast cancer.[25] Trastuzumab's targeting of the human epidermal growth factor receptor 2 (HER2) is the most effective example of targeted treatment in MBC. In HER2- positive trastuzumab-resistant breast cancer, dual and irreversible HER2/epidermal growth factor receptor targeting and inhibition of downstream resistance pathways also seem promising. Targeted treatment with antiangiogenic drugs exhibits clinical action, but the trade-off between effectiveness, toxicity, and cost is still up for dispute, highlighting the unmet need for a biomarker that can predict how well a patient would respond to this type of medication.[26] The proper patient selection for immunotherapy research and integration into clinical practice may be influenced by the integration of several putative biomarkers and consideration of dynamic markers of early response or resistance.27 The immune system has a complicated function in the early detection and elimination of cancer as well as its development. Checkpoint inhibitors and chimeric antigen receptor T cell therapy have now entered the clinic, with impressive and durable clinical responses seen across a broad array of tumor types. The development of an immune focused strategy for treating breast cancer is supported by a number of lines of

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evidence.28To target and visualize metastatic breast cancer, both macroscopic and microscopic NPs have been developed. In this perspective, the NPs must have tumor specific ligands and are able to increase the detectability of imaging modalities. It is possible to choose certain ligands for the identification of probable metastases with the right molecular profiling of tumor tissues.29 Neoadjuvant chemotherapy may be given via combination treatments. In a phase II neoadjuvant research, docetaxel and epirubicin were used to examine the effectiveness and safety of treating individuals with inflammatory breast cancer as well as those with large, operable, or locally advanced (Stage III) breast cancer. The trial's findings revealed a 76.7% observed response rate.30 The most difficult breast cancer subtype to treat is triple-negative breast cancer (TNBC). Chemotherapy continues to be the gold standard of treatment since medicines that target particular molecular targets have only sometimes improved the outcomes of people with TNBC clinically meaningfully.31 Pembrolizumab recently showed encouraging outcomes in early- stage TNBC, which may soon result in its approval in (neo) adjuvant settings[32]. De novo small-molecule medicines that specifically target distinct molecular features of TNBC may provide a potential treatment for the disease.

A single-target drug discovery that is perfect still has a lot of work to do. Alternately, new developing approaches such medication repurposing, dual-targeting, and combination methods may offer fresh perspectives on how to enhance TNBC therapies as depicted in the Figure 2 below.[33-37]

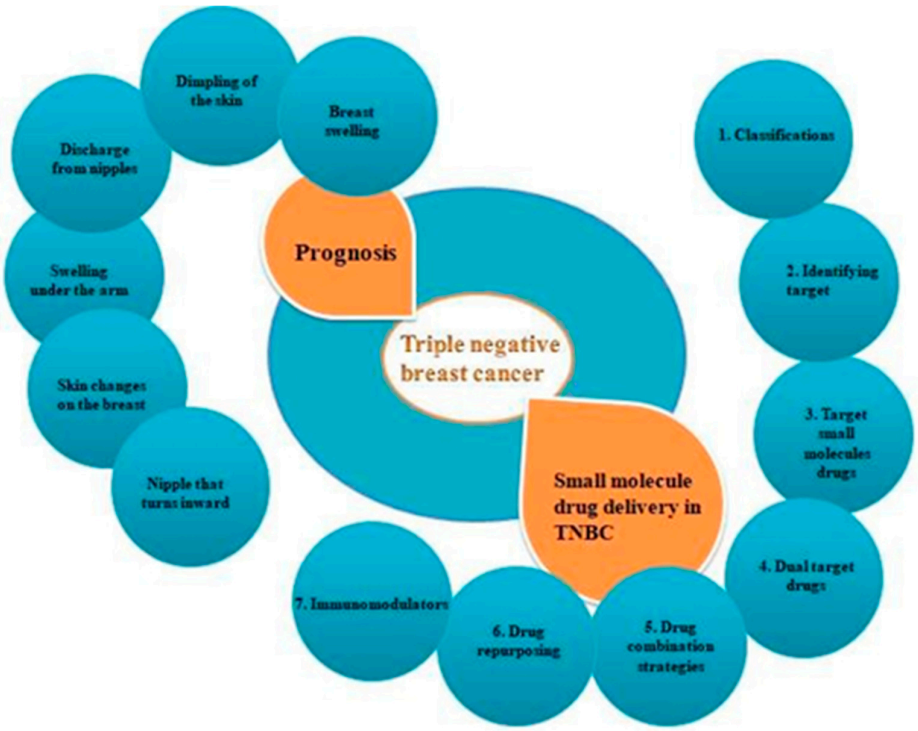

Figure 2. Diagram shows the symptoms for prognosis and Small molecule drug delivery process in Triple-negative breast cancer.

5. Treatment with nanocarriers

a) Dendrimers

Dendrimers are promising drug delivery technologies that can get beyond the drawbacks of the anticancer medications currently in use. They can combat medication resistance, minimize drug toxicity, increase drug solubility, and boost drug bioavailability. The dendrimers' drug release profiles were often sustained within physiological situations, which led to their low toxicity to healthy cells and their rapid drug release under tumour conditions, which led to high cytotoxicity and absorption in the breast cancer cells.38 Treatment with nanocarriers, particularly dendrimers, has emerged as a promising avenue in drug delivery due to their unique structural properties and

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versatile surface functionalities. Dendrimers are highly branched macromolecules with well-defined sizes and shapes, allowing for precise control over drug loading and release kinetics. These nanocarriers offer several advantages, including enhanced drug solubility, improved bioavailability, and targeted delivery to specific cells or tissues. The dendritic architecture of these nanocarriers enables the incorporation of various therapeutic agents, such as anticancer drugs, imaging agents, and gene therapeutics. Additionally, their modifiable surface chemistry allows for the attachment of ligands, facilitating targeted delivery and minimizing off-target effects. Notably, studies by Svenson and Tomalia have highlighted the potential of dendrimers in drug delivery, emphasizing their role in overcoming challenges associated with traditional drug formulations. Furthermore, the work of Wu et al. underscores the importance of dendrimers in enhancing the efficacy and safety of therapeutic agents, showcasing the significant strides made in the field of nanomedicine through the use of dendrimer-based nanocarriers. The exploration of dendrimers as nanocarriers continues to evolve, holding promise for the development of innovative and effective treatments across various medical applications [39,40]. Dendrimers, which are highly branched and well-defined large molecules, demonstrate distinct characteristics and potential applications across various domains. To grasp their fundamental principles, it is crucial to explore their structure and how they function. Recent research has revealed that dendrimers possess a tree-like design comprising a central core, branched arms, and functional end groups[41] .41 These nanoscale structures are painstakingly crafted, enabling precise manipulation of their size, shape, and surface attributes.

The functionality of dendrimers is multifaceted. They can enclose drugs or other substances within their interior, shielding them from degradation and improving delivery[42] 42 Moreover, thanks to their adjustable surface properties, dendrimers can target specific cells or tissues, making them highly promising for drug delivery applications[43].95The research delved into the investigation of exocytosis dynamics, pathways, and mechanisms of PAMAM dendrimers in multidrug-resistant tumor cells. The study focused on three PAMAM dendrimers with distinct surface charges—positively charged PAMAM-NH2, neutral PAMAM-OH, and negatively charged PAMAM-COOH. Utilizing a multidrug-resistant human breast cancer cell model (MCF-7/ADR), the researchers observed the potential to develop a surface-charged drug delivery system targeting tumors, particularly effective in transfecting treatment-resistant cells. The administration of SiRNA-MVP or an inhibitor emerged as a strategy to decrease MVP-mediated nuclear efflux, enhancing DNA transfection efficiency with PAMAM-NH2.

Comparative analyses were conducted with sensitive breast cancer cells (MCF-7 cells) serving as the control. The investigation encompassed cellular uptake, intracellular transportation, and efflux of PAMAM-NH2 dendrimers in multidrug-resistant breast cancer cells (MCF-7/ADR cells). Notably, PAMAM-NH2 exhibited reduced absorption rates from P-glycoprotein and multidrug resistance-associated protein in MCF-7/ADR cells, resulting in significantly higher exocytosis and lower endocytosis compared to MCF-7 cells. P-gp and MDR-associated protein were identified as factors contributing to the observed differences in PAMAM-NH2 exocytosis and endocytosis between the two cell types, with macropinocytosis playing a more substantial role in subsequent cells.

In a separate study, iron oxide nanoparticles (IONPs) were functionalized with fourth-generation (G4) polyamidoamine (PAMAM) dendrimers to address breast cancer in BALB/c mice through magnetic hyperthermia. Exposure to an alternating magnetic field (AMF) and incubation with G4@IONPs resulted in a significant reduction in the lifespan of breast cancer cells, attributed to apoptosis and an increased Bax/Bcl-2 ratio. This study demonstrated that magnetic hyperthermia therapy reduced tumour angiogenesis and increased cancer cell apoptosis, both of which suppressed tumour growth[44].41 Dendrimers, a group of highly branched polymers, can be meticulously designed to envelop both anti-cancer medications and targeting molecules, facilitating the precise delivery of drugs to cancerous regions. A study conducted by Chauhan and colleagues in 2018 illustrates the improved ability of dendrimer-based drug delivery systems to specifically target tumors[45].100

a) **Nano emulsion**

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Nanoemulsions consist of tiny droplets of one liquid dispersed in another liquid that don't mix well, and they are kept stable by surfactants or similar molecules with both hydrophilic and hydrophobic properties. Nanoemulsions are highly adaptable and come with numerous benefits, such as improved solubility, bioavailability, and the stability of different substances.

The nanoemulsion structure comprises an oil phase that encapsulates lipophilic compounds, a water phase that solubilizes hydrophilic components in the continuous aqueous medium, and surfactants that encircle the oil droplets to inhibit coalescence. This arrangement operates by reducing droplet size to the nanometer scale, thereby increasing the surface area available for interaction with biological substrates. It enhances the solubility of hydrophobic substances within the oil phase, aiding in their delivery and promoting improved bioavailability through enhanced cellular uptake and absorption of the encapsulated contents. Additionally, the inclusion of surfactants plays a crucial role in maintaining prolonged stability by preventing the aggregation of droplets, thereby extending the shelf life as indicated in references [96,97]. In a prior study, the antioxidative capabilities of a nanoemulsion containing elemene were assessed through Electron Spin Resonance (ESR) measurements and quantum mechanical simulations. To establish a mouse model for Triple-Negative Breast Cancer (TNBC), BalB/c mice underwent subcutaneous injections of the murine breast cancer cell line 4T1 into the left fourth mammary fat pad. The therapeutic effects of the elemene nanoemulsion on mice with TNBC were evaluated using diverse methods, including Hematoxylin and Eosin (H&E) staining, immunohistochemical staining, Dihydroethidium (DHE) staining, and Western blot analysis. As a result of its ability to scavenge ROS, elemene nanoemulsion efficiently prevented breast cancer cells from spreading to the liver and lung, which in turn increased the survival time of TNBC mice.48 Another study prepared an LAP-loaded nanoemulsion (NE- LAP) with the intention of testing its anticancer effectiveness. For this, a hot homogenization technique was used to create the nanoemulsion, and cryogenic transmission electron microscopy was used to analyse the nanoemulsion's morphology (cryo-TEM). The effective preparation and characterization of NE-LAP revealed the necessary characteristics to support intravenous delivery. The 30-day short-term stability of NE-LAP at 0.5 mg/mL was shown, and drug release experiments showed a more sustained release profile. Studies on biodistribution and blood clearance support the hypothesis that longer blood circulation times result in preferential tumour absorption. These enhancements undoubtedly played a role in the increased antitumor activity seen for NE-LAP compared to LAP alone.Its positive performance, together with the lack of toxicity symptoms, encourages us to recommend NE-LAP as a successful cancer therapy method.[43].

A different research based on the conventional nanoemulsion and employing the idea of long-circulation targeting receptor mediated, a folate-targeted nanoemulsion (folate/PEG-DSPE/nanoemulsion, FNEs) was created. In order to create the nanoemulsion (folate/PEG-DSPE/nanoemulsion, or FNEs), high-pressure homogenization with a microfluidizer was used. This work has the potential to significantly increase the therapeutic efficacy of chemotherapy medications used to treat cancers and offers a helpful reference for addressing the issue of chemotherapy treatments' subpar clinical efficacy. Graphical Abstract A schematic picture of the folic acid/PEG-DSPE/nano-emulsion (FNEs) shows how the combination selectively targets tumour cells and has stronger anti-tumor effects.[44][50]. In a separate study, researchers enhanced the composition of nanoemulsion to co-encapsulate paclitaxel and elacridar. Their chosen nanocarrier demonstrated favorable qualities and short-term stability, leading to increased cytotoxicity of paclitaxel. The presence of elacridar further augmented this effect in both 2D and 3D models. Additionally, elacridar reduced the amount of nanoemulsion required to inhibit P-glycoprotein (P-gp) ATPase function. Modification of nanoemulsions with hyaluronic acid (HA) extended the in vivo retention of rhodamine, incorporated in NETri. The results indicate that the developed nanoemulsion effectively delivers elacridar and paclitaxel to cancer cells, enhancing the therapeutic efficacy of paclitaxel, particularly in triple-negative breast cancer cell lines. The study's significant application lies in improving treatment outcomes for triple-negative breast cancer therapy options are limited, providing fresh opportunities for research into novel therapeutic approaches to treat the condition.[45] Nanoemulsions, which are extremely tiny droplets of oil dispersed in water or water dispersed in oil,

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can enhance drug solubility and stability. These minuscule droplets have the capacity to encapsulate medications and selectively target tumor tissues, thereby improving the precision of drug delivery. Research conducted by He and colleagues in 2020 underscores the promising prospects of nanoemulsions in the realm of targeted drug delivery.[101]

a) **Carbon Nanotubes**

Carbon nanotubes (CNTs) are elongated carbon structures possessing extraordinary characteristics, and comprehending their fundamental principles is crucial. CNTs possess distinctive mechanical, electrical, and thermal properties due to their hexagonal lattice configuration. Single-walled CNTs (SWCNTs) are composed of a single layer of graphene rolled into a cylindrical shape, while multi-walled CNTs (MWCNTs) consist of multiple concentric layers. To exemplify the underlying principles and mechanisms, we can turn to recent research. For instance, a study conducted by Liu et al. in 2021 provides insights into the growth processes of SWCNTs and MWCNTs, shedding light on catalytic mechanisms and the significance of catalyst nanoparticles. Furthermore, the research conducted by Wang et al. in 2022 underscores the electronic structure and conductivity of CNTs, which are the foundations of their exceptional electrical characteristics.98,99[53, 54] CNTs have been employed as nanocarriers to transport chemotherapeutic proteins, genes, and anticancer medications through suitable functionalization. In order to obliterate cancer cells directly, they have also been used as mediators for photothermal therapy (PTT) and photodynamic therapy (PDT).46[55]. In photothermal therapy (PTT), carbon nanotubes (CNTs) serve as agents that can be precisely directed to cancer cells and cause them to heat up when exposed to near-infrared light. This localized increase in temperature effectively harms and eliminates cancer cells. On the other hand, photodynamic therapy (PDT) involves the activation of photosensitizers, often connected to CNTs, using specific light wavelengths. This activation leads to the production of reactive oxygen species, which can trigger cell death in targeted cancer cells. Recent research, exemplified by the work conducted by Yang et al. in 2021, underscores the promising potential of CNTs in PTT and PDT, highlighting their role as innovative approaches for treating cancer. In a previous study, a nanoconjugate made of single-walled carbon nanotubes functionalized with carboxyl groups (SWCNT-COOH) and cisplatin (CDDP) was created in a prior study to investigate the possibility of blocking the PI3K/Akt signalling pathway. Inhibiting breast cancer cell migration, downregulating PI3K/Akt signalling, and promoting cell death are all effects of CDDP conjugated with SWCNT-COOH that are highly potential and may help in the creation of new methods for the targeted treatment of breast cancer that is both highly proliferative and metastatic.Conjugated single-walled carbon nanotubes (SWNT) are biocompatible, quickly excreted, and have little toxicity, making them potential for cancer-targeted accumulation.46 [55]. The focus of the study was to evaluate the developments in carbon nanotubes, particularly SWNT, for treating breast cancer. Future tumour therapy with low drug doses may benefit from the great efficacy and minimal adverse effects of nanotube drug delivery systems. It demonstrates how we now understand the interaction between cells and their surroundings. It has been demonstrated that CNTs, and more especially SWNTs, can mimic the natural ECM to help cells adhere to one another and control gene expression. This field of study offers a brand-new approach to identifying and treating breast cancer.47[56].

In a different study, they used molecular dynamics simulations to look at the binding properties of single-walled carbon nanotube and glycated chitosan. The investigation delved into the mean square displacement, radius of gyration, interaction energy, and radial distribution function of the system comprising single-walled carbon nanotubes (SWNTs) and glycated chitosan. Results from molecular dynamics simulations revealed a robust noncovalent association between glycated chitosan and single-walled carbon nanotubes.48[57]. The primary focus of the study was the careful selection of suitable SWNTs and GC polymer to construct an efficient multifunctional nanosystem (SWNT-GC) for biomedical applications. The analysis specifically explored the binding characteristics of the SWNT-GC nanosystem, considering SWNTs with diverse chiralities, diameters, and lengths, along with glycated chitosan of varying properties..48 [57]. The inability to adjust the RU-length of the GC polymer is one of the constraints in experimental research when examining a functionalized SWNT system, specifically SWNT- GC.Doxorubicin (DOX) and paclitaxel (PTX), two

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commonly used anticancer medications, have unique physicochemical characteristics and chemotherapeutic specificity. All-atom molecular dynamics (MD) simulations for various SWCNT systems were initially conducted in order to explore their interaction mechanism with single-walled carbon nanotubes (SWCNTs), co-loading and releasing from the SWCNTs, and then binding free energy calculations with MM-PBSA. The outcomes show that the exothermic and spontaneous co-loading of DOX and PTX onto the pure SWCNT. It comes to the conclusion that the coloading and release of DOX and PTX via the f-SWCNT is conceivable.49 [58].

In a prior study, a proposed dual-responsive smart carrier, sensitive to both pH and temperature, comprised functionalized single-walled carbon nanotubes (SWNT) and single-walled carbon nanotubes (SWCNT) grafted with dimethyl acrylamide-trimethyl chitosan (DMAA-TMC). Molecular simulations were employed to investigate the carrier's drug affinities and interaction energies with doxorubicin (DOX) and paclitaxel (PAX). The carrier exhibited selective and sensitive drug delivery for DOX and PAX in both healthy and malignant conditions, as indicated by energy analysis of drug release and adsorption. The interaction between DMAA-TMC, a biodegradable and biocompatible copolymer, and SWCNT revealed copolymer distortion during degradation in an acidic environment, facilitating a smart release mechanism in acidic malignant tissues. This approach improved hydrophilicity, achieved an optimal nanoparticle size, and addressed cell cytotoxicity concerns.50[59].

In a separate investigation, multiwalled carbon nanotubes (MWCNTs) were synthesized using lysine as a linker and functionalized with carbohydrate ligands. This method facilitated effective doxorubicin (Dox) delivery to breast cancer cells through targeted mechanisms. MWCNTs, being elongated hollow cylindrical nanotubes of sp2 carbon, gained attention in drug delivery due to their substantial surface area and high drug-loading capacity. The use of lysine as a linker enabled a cost-effective method for functionalizing MWCNTs with carbohydrate ligands such as galactose (GA), mannose (MA), and lactose (LA). Characterization through FT-IR, NMR, Raman, XRD, and FE-SEM confirmed the successful functionalization of MWCNTs loaded with Dox. In vitro assessments on drug-loaded MWCNTs in breast cancer cells, including drug loading, release, and cell toxicity, demonstrated that carbohydrate-modified lysinated MWCNTs, particularly LyMWCNTs, exhibited higher Dox loading capacity compared to carboxylated MWCNTs (COOHMWCNTs) and lysinated MWCNTs. Notably, LyMWCNTs displayed a sustained release profile of Dox, releasing more drug over 120 hours at pH 5.0, indicative of their potential as candidates for targeted drug delivery in the tumor microenvironment.51 [60]. Carbon nanotubes (CNTs) exhibit distinct physicochemical characteristics that can be harnessed for drug delivery and imaging purposes. In the study conducted by Kostarelos and colleagues in 2018, they delve into the precise targeting of CNTs for treating tumors. Integrating these innovative therapeutic methods into your review paper will provide insight into their potential for targeted tumor therapy and the encouraging advancements in this field.102 [61].

b) **Nanoparticles**

Nanoparticles, which are typically sized between 1 and 100 nanometers, possess unique characteristics at the nanoscale that have led to innovative approaches in the treatment of breast cancer. These minuscule structures can be designed to transport and administer drugs with precision, offering several advantages. For example, drug delivery systems based on nanoparticles can enhance the solubility and stability of anticancer medications, extend their circulation in the body, and facilitate targeted delivery to cancerous tissue. This targeted drug delivery reduces unwanted side effects and boosts the effectiveness of breast cancer treatments.

Recent studies have underscored the potential of nanoparticles in the context of breast cancer therapy. For instance, in 2020, Wang et al. explored the use of nanoparticles to precisely deliver chemotherapy drugs to breast cancer cells, emphasizing the improved efficacy of the drugs and the reduction in side effects. Another investigation in 2021 by Guo et al. delved into the utilization of nanoparticles in photothermal therapy for breast cancer, showcasing their efficiency in eradicating cancer cells.104,105 [62, 63].

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With the selective targeting and distribution of these anticancer medications to tumour tissues, nanotechnology has traditionally been used in cancer therapy to enhance the pharmacokinetics and lower the systemic toxicities of chemotherapies. Multiple studies use different types of nanoparticles with effective chemotherapy to treat different types of cancers including breast cancer.

Prior research focused on targeting the epidermal growth factor receptor (EGFR) through the conjugation of bovine serum albumin (BSA) with cetuximab-valine-citrulline (vc)-doxorubicin (DOX), facilitating the release of the medication specifically into tumor cells overexpressing EGFR. The findings indicate that cetuximab-vc-DOX-NPs represent a viable strategy for targeted drug delivery, exhibiting favorable tumor-targeting capabilities while minimizing systemic toxicity. This study underscores the therapeutic potential of cetuximab-vc-DOX-modified BSA nanoparticles against EGFR-expressing cancers.52 [64].

An alternative promising approach for efficient chemotherapy involves pairing a specific targeting antibody with an anticancer drug on a nanoparticulate platform. Through the modification of bovine serum albumin (BSA), a stimuli-responsive system for drug administration and controlled release was developed. Utilizing the desolvation method, doxorubicin (DOX)-loaded BSA nanoparticles (NPs) were easily generated, followed by crosslinking with Schiff base bonds to create pH-sensitive DOX-loaded systems (DOXs@BSA NPs). The resulting DOXs@BSA NPs exhibited a substantial drug loading capacity (21.4%), with a size of approximately 130 nm, narrow polydispersity, and a strongly negative surface charge (-20.5 mV). Alterations in size and charge observed after incubation at different pH levels provided evidence of the pH sensitivity of the DOXs@BSA NPs. .The pH-responsive characteristic of carbonate apatite (CA) particles allows for quick intracellular drug release, however they are often heterogeneous and have a propensity to self-aggregate.53[65]. Here, they modified the nano-carrier by partially replacing Ca^{2+} with Mg^{2+} and Fe^{3+} into a fundamental CA lattice, resulting in Fe/Mg-carbonate apatite (Fe/Mg-CA) NPs with the ability to reduce self-aggregation, form a distinctive protein corona in the presence of serum, and effectively deliver the anti-cancer drug doxorubicin (DOX) into breast cancer cells. Fe/Mg- CA, which mostly forms a protein corona linked to transport proteins, may therefore be an effective carrier for therapeutic administration in breast cancer.The earlier research revealed that compared to CA NPs, both low Fe/Mg-CA and high Fe/Mg-CA NPs have a nano-sized dimension with improved homogeneity and a potential ability to mitigate self-aggregation. This results in improved drug binding, more efficient cellular uptake of drug-loaded NPs, and a higher cytotoxic effect on the cancer cells. These findings were consistent with the protein corona analysis, which demonstrated interactions between dysopsonins and DOX-loaded CA, low Fe/Mg-CA, and high Fe/Mg-CA NPs, extending their blood circulation times and preventing the blood's hepatic degradation of the drug cargo before it reaches the tumour site. Fe/Mg-CA NPs, particularly those with high Fe/Mg ratios, show promise as a means of delivering anti-cancer medications, including for the treatment of breast cancer.54[66].

A different study created two brand-new, self-assembling nanoparticles that contained DOX without the usage of hazardous chemicals or chemical processes. Although BC-DOX-NPs were produced by the adsorption of BSA on the surface of BC-DOX-NPs, CS-DOX-NPs were created based on interactions between positive and negative charges. Both formulations demonstrated superior stability and prolonged release, efficient CD44 targeting, and improved cell uptake in vitro. In vivo, BC-DOX-NPs outperformed CS-DOX-NPs, exhibiting improved tumor-specific distribution and penetration that led to improved anticancer activity in a 4T1 mouse model. It demonstrates BC-DOX-NPs' potential for active targeted tumour therapy, and their straightforward manufacture may make them more useful for commercial applications.55[67].

In a recent study, the effective delivery of the anthracycline medication doxorubicin (DOX) into breast cancer cells was successfully achieved using goose bone ash (GBA) as a pH-responsive carrier. Specifically, MCF-7 and MDA-MB-231 cells were targeted in this investigation. The characteristics of GBA, including size, shape, functional groups, cellular internalization, cytotoxicity, pH-responsive release of DOX, and analysis of the protein corona, were thoroughly examined in both its pure form and in suspension.

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The study revealed a dose-dependent increase in the binding affinity between DOX and GBA, indicating a heightened effectiveness with higher DOX concentrations. Notably, GBA particles exhibited no intrinsic toxicity, as evidenced by cell viability and cytotoxicity analyses. Qualitative and quantitative assessments of cellular uptake in the two cell lines, MCF-7 and MDA-MB-231, demonstrated that the internalization of DOX-loaded GBA surpassed that of free DOX molecules.

Furthermore, the results suggested that employing GBA as a carrier enhances cellular internalization and improves the effectiveness of drug binding. Importantly, in vitro cytotoxicity analysis confirmed the ability of DOX-loaded GBA particles to effectively halt the proliferation of breast cancer cells, including MCF-7 and MDA-MB-231 cells.

A key finding of the study highlighted the pH-responsive nature of GBA, releasing DOX under acidic conditions (endosomal/lysosomal pH: 6.5–5.5) while remaining stable at physiological pH (pH 7.5). This pH-responsive behavior contributes to the potential therapeutic efficacy of GBA in the targeted treatment of breast cancer cells.

Polymeric nanoparticles

Several illness treatments have showed promise when using cell membrane as a surface covering. Nanoparticles with cell membrane coatings have improved immune-compatibility and longer circulation times. A targeted nano-therapy for combating cancer has been devised by employing nanoparticles enveloped in human red blood cell (RBC) membranes, enhancing their targeting precision. The nanoparticles consist of polymeric cores housing both chemotherapy agents and imaging substances. To augment their targeting capabilities, the naturally derived human RBC membranes have been modified with attached targeting ligands. This innovative theranostic platform, termed nature-inspired targeted human red blood cell membrane-coated polymeric nanoparticles (TT-RBC-NPs), demonstrates the ability to specifically adhere to cancer cells, facilitate the efficient delivery of doxorubicin (DOX), and enable visualization of targeted cancer cells, exemplified by the use of epithelial cell adhesion molecule (EpCAM)-positive MCF-7 breast cancer cells as a representative disease model. The utilization of biomaterials characterized by low immunogenicity, exceptional biocompatibility, and prolonged circulation periods serves as an effective stealth shield for drug delivery systems, evading immune system detection and generating increasing interest in the field.The key characteristics and functioning of the membrane cells are more easily transferred to the core of the nanoparticle when they are coated with an RBC cell membrane.57

In a recent study, the investigation of LINC01094, microRNA (miRNA, miR)-340-5p, and E2F transcription factor 3 (E2F3) expressions in breast cancer (BC) tissues and cells utilized Western blot and quantitative real-time polymerase chain reaction (qRT-PCR). LINC01094 was identified to modulate the miR-340-5p/E2F3 molecular axis, promoting BC cell proliferation and advancing cell cycle progression while suppressing apoptosis. Through its impact on the miR-340-5p/E2F3 molecular axis, LINC01094 facilitated cell cycle progression, stimulated BC cell proliferation, and hindered apoptosis. This research provides insights that could be valuable for early BC diagnosis, prognostic evaluation, and gene therapy.58 [69]. In another investigation, the functions of miR-16-5p and ANLN in BC were explored. The effects on cell proliferation, migration, invasion, cell cycle, and apoptosis were assessed using MTT, wound healing, Transwell invasion, and flow cytometry, respectively. Results suggest that miR-16-5p modulates ANLN, suppressing proliferation, migration, and invasion while influencing the cell cycle and promoting apoptosis. These findings propose novel potential biomarkers for the detection and treatment of BC.59[70]. MicroRNA-135a-5p (miR-135a-5p) has been observed to influence the behavior of Breast Cancer (BC) cells. To assess the levels of miR-135a-5p and Bcl-2 Associated Athanogene (BAG3) expression in BC tissues and cells, respectively, quantitative real-time PCR and western blot analyses were employed. The proliferation, migration, invasion, and cell cycle of BC cells were investigated using the cell counting kit-8 assay, the BrdU assay, the wound healing assay, the transwell assay, and flow cytometry. In BC tissues, there was a noticeable increase in BAG3 expression and a corresponding decrease in miR-135a-5p expression. The impact of miR-135a-5p on the malignant characteristics of BC cells was nullified upon BAG3 overexpression. Elevated BAG3 expression activated the cell cycle, mTOR, and TGF-signaling

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pathways in BC cells. It was demonstrated that miR-135a-5p regulates BAG3, thereby impeding the growth, migration, invasion, and progression through the cell cycle of BC.60[71].

Magnetic nanoparticles

Magnetic nanoparticles have garnered significant attention as a promising means of delivering drugs precisely to cancer cells. They operate by responding to an external magnetic field. These nanoparticles are often filled with chemotherapy drugs and, when subjected to a magnetic field, are directed to specific areas of interest, such as metastatic organs. Recent research, exemplified by Estelrich and colleagues in 2015, clarifies how magnetic nanoparticles can be tailored to transport drugs and guide them to metastatic locations using magnetic fields. Once they arrive at the target, the nanoparticles release their cargo, enabling localized drug delivery. This method reduces unintended side effects and increases the concentration of therapeutic agents at the tumor site, providing a more efficient and precisely targeted treatment approach. Curcumin-naringenin loaded dextran-coated magnetic nanoparticles (CUR-NAR-D-MNPs) were employed as chemotherapy and in combination with radiotherapy to demonstrate their efficacy in treating tumours, which improved the effectiveness of cancer treatment. To determine how CUR- NAR-D-MNPs would work in conjunction with radiotherapy in the treatment of malignancies, they were created and put to the test in vitro and in vivo. With good biocompatibility, the nanomaterial can promote ROS, direct tumour cell death, and prevent tumour cell multiplication.61[72]. In a prior investigation, the efficacy and safety of novel nanoparticles enabling the simultaneous administration of DOX and curcumin for treating invasive B cell lymphoma were evaluated both in vitro and in vivo. The study employed mPEG-b-P(Glu-co-Phe) polymer nanomaterials to co-deliver curcumin (CUR) and DOX, termed L-DOX + CUR. Utilizing flow cytometry to quantify the DOX signal allowed for an assessment of the drugs' cellular penetration. Additionally, confocal microscopy was employed to observe various cell enrichment regions directly. The study demonstrated that the high molecular weight mPEG-b-P(Glu-co-Phe) co-loaded with doxorubicin and curcumin exhibited low toxicity and a potent anti-lymphoma effect. These findings support the utilization of polymeric nanoparticles for delivering traditional chemotherapeutic agents, providing a conceptual basis for employing synergistic medications in lymphoma treatment.62[73].In order to treat a breast cancer model in Balb/c mice, a dual-functioned nanocomposite (NC) was also created. This NC used both photodynamic and photothermal techniques. The nanostructure, silica coating, and curcumin (CUR) immobilisation on the Fe3O4 nanoparticles were validated by transmission electron microscopy, UV-visible spectroscopy, FTIR, and XRD. In a breast tumour mouse model, the impact of Fe3O4/SiO2-CUR in combination with PDT and PTT was evaluated in vivo. Immunohistochemistry (IHC) was used to assess the expression of apoptotic Bax and Caspase3 proteins. Because they have few therapeutic choices, triple-negative breast tumours, which we employed as our study's model, are widely known to be highly invasive.As a result, our data suggested that the NC + PDT + PTT approach would provide a promising alternative to chemotherapy for the treatment of triple-negative breast tumours. These outcomes made us understand that there is a good chance that this dual irradiation approach will eventually replace the current, dangerous therapeutic treatments.63[74]. In another study, effective macrophage activation for anticancer immunotherapy has two main obstacles. First, cancer cells are prevented from being phagocytosed by macrophages when the signal regulatory protein alpha (SIRP) on macrophages is bound to CD47, a "don't eat me" signal on cancer cells. Second, tumor-associated macrophages (TAMs) get polarised to a tumorigenic M2 phenotype by colony promoting substances released by cancer cells. Here, it is claimed that magnetic nanoparticles with cell membrane coatings created through genetic engineering (gCM-MNs) can block both pathways. A combination of the MN core promoting M2 TAM repolarization and the gCM shell genetically overexpressing SIRP variants with remarkable affinity effectively blocks the CD47-

The activation of the SIRP pathway has been observed to induce potent immune responses in macrophages.64,65 [75,76]. Utilizing a combination of cell membrane coating nanotechnology and genetic editing technology has proven to be a safe and effective strategy to stimulate the body's immune responses for cancer immunotherapy. Currently, four main categories of magnetic

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nanoparticle (MNP) utilization in breast cancer include Sentinel lymph node biopsy (SLNB), medication delivery systems, magnetic hyperthermia, and imaging of primary and metastatic illnesses. There is increasing evidence supporting the application of MNPs in these areas, with emerging clinical uses, particularly in breast oncological surgery. MNPs have been employed through various methods, including imaging, medication administration, and magnetic hyperthermia, to detect nonpalpable lesions. These disciplines are still evolving rapidly. Yet, SLNB for breast cancer and malignant melanoma is currently achieving the surgical uses of MNPs.66[77].

Metallic nanoparticles

Researchers have developed a multifunctional nanovehicle to enhance drug delivery and cancer cell imaging, specifically for breast cancer. This nanovehicle consists of porous silicon nanoparticles combined with gold nanorods (composite nanoparticles or cNPs), enclosed within a hybrid polymersome using double-emulsion templates on a microfluidic device. Administered intravenously in mice, the nanovehicle efficiently accumulates at the tumor site, demonstrating excellent loading capacity for both hydrophobic and hydrophilic drugs. Notably, a triple-drug combination, delivered at total dosages of 5 and 2.5 mg/kg, reduces breast cancers by 94% and 87%, respectively. This research highlights the potential of the nanovehicle as a versatile drug delivery platform for combination therapy across various cancer types and biological targets associated with disease development.676[78].

In another study, researchers investigated the use of polymersomes as carriers for recoiling daughters of 225Ac, evaluating their therapeutic potential. Intravenous injection of 225Ac-containing vesicles in both healthy and tumor-bearing mice revealed the redistribution of free 213Bi in various organs. The study also examined the therapeutic efficacy of intratumorally injected 225Ac-containing vesicles, demonstrating no tumor-related fatalities in the treatment groups over 115 days. While polymersomes containing 225Ac show promise for long-term tumor irradiation without significant kidney damage, careful assessment of the impact of daughter nuclides in targeted alpha therapy is crucial.687 [79].

❖ **Platinum**

Platinum nanoparticles (PtNPs) were investigated for their potential as radiosensitizers in two breast cancer cell lines, T47D and MDA-MB-231, which exhibit varying radiation sensitivities. Following PtNP ingestion, the nanoparticles were localized in lysosomes and multivesicular bodies within the cells. Contrary to findings in a previous study involving cervical cancer HeLa cells under identical conditions, pre-exposure of T47D and MDA-MB-231 cells to PtNPs before radiation did not show any discernible enhancements in clonogenicity, survival, mortality, cell-cycle distribution, oxidative stress, or DNA double-strand breaks. This underscores the substantial impact of cell type on the effectiveness of radio-enhancement by PtNPs. The study concludes that PtNPs exhibit a high degree of cell-dependent variability in their ability to enhance radiation effects, with no observable impact on the investigated breast cancer cell lines. This research confirms how strongly cancer cells influence the success of combination therapies.69[80].

❖ **Palladium**

In this research, the utilization of an extract derived from the medicinal plant Gloriosa superba tuber is presented, marking the inaugural exploration of the anticancer properties associated with phytogenic platinum nanoparticles (PtNPs) and palladium nanoparticles (PdNPs) found in GSTE (Gloriosa superba tuber extract).The formation of dark brown and black colours for PtNPs and PdNPs, respectively, as well as an improvement in the peak intensity in the UV-visible spectra, respectively, served as evidence that the nanoparticle synthesis was finished in less than 5 hours at 100°C. The effectiveness of phytogenic production of nanoscale platinum and palladium medicines for the treatment and management of breast cancer is supported by these studies.Using

G. superba tuber extract, monodispersed PtNPs and PdNPs were created, and they were reported to be consistently spherical and almost isodiametric. It was discovered that the synthesis was quick, effective, and safe for the environment. With regard to MCF-7 (human breast adenocarcinoma) cells, PtNPs and PdNPs both shown strong anticancer activity. The induction of

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apoptosis, which is characterised by phosphatidyl serine externalisation, membrane breakdown, and blebbing with chromosomal condensation, has been identified as the mechanism of cell death.70 [81].

❖ **Gold**

Gold nanoparticles (GNPs) have been employed to enhance the absorbed dose administered to cancer cells and sensitize them, with minimal impact on healthy cells. Active targeting, specifically the conjugation of GNPs with the AS1411 aptamer (AS1411/GNPs), aims to achieve a targeted effect, increasing GNP uptake in malignant cells. This study aimed to investigate the potential radiosensitization of cancer cells exposed to 4 MeV electron beams using AS1411/GNPs. The AS1411 aptamer facilitated improved distribution of gold nanoparticles within cancer cells, resulting in enhanced radiation-induced cancer cell death. Clonogenic assay results and Au cell uptake findings indicated that the AS1411 aptamer contributed to increased radiation-induced cell death by augmenting Au uptake. Notably, the enhanced sensitivity induced by AS1411 aptamer-conjugated GNPs rendered cells resembling cancer stem cells more responsive to 4 MeV electron beams. Gold nanoparticles exhibit a unique capability to selectively target tumor cells over normal ones, referred to as active targeting. This selectivity can be attributed to several factors. To begin with, tumor cells tend to display higher rates of cell division and increased blood vessel formation, resulting in leakier and more chaotic blood vessel structures. This phenomenon, known as the enhanced permeability and retention (EPR) effect in tumor blood vessels, enables GNPs to accumulate more within the tumor's environment. Additionally, modifying the surface of GNPs by attaching targeting molecules like aptamers or antibodies can further enhance their specificity for tumor cells. These molecules recognize specific markers that are overexpressed on the surface of cancer cells, facilitating the uptake of GNPs by malignant cells. For instance, research conducted by Li et al. in 2018 has demonstrated the potential of the AS1411 aptamer to increase GNP uptake in cancer cells, leading to improved cell death when exposed to radiation. This active targeting approach leverages the unique features of tumor microenvironments and cancer cell surfaces to enhance the therapeutic effectiveness of GNPs while minimizing their impact on normal cells.107, 108 [82,83]

❖ **Copper**

A safe, copper-depleting nanoparticle (CDN) that targets the mitochondria is created in a prior study and tested against triple-negative breast cancer (TNBC). They demonstrate that CDNs trigger a metabolic switch to glycolysis, lower ATP synthesis, and decrease oxygen consumption and oxidative phosphorylation in TNBC cells. Apoptosis is brought on by this lack of energy, damaged mitochondrial membrane potential, and increased oxidative stress. In healthy mice, we show that CDNs are not harmful. The injection of CDN suppresses tumour growth and significantly increases survival in three mice models of TNBC. The effectiveness and safety of CDNs point to the potential clinical utility of this strategy.71

❖ **Silver**

A research study aimed to assess the capability of silver nanoparticles (AgNPs) in inhibiting the metastatic potential of breast cancer cells by inducing epithelial-to-mesenchymal transition (EMT). Various methods, including the sulforhodamine B assay, wound healing test, measurement of reactive oxygen species (ROS) production, conventional cytofluorimetric analysis of the cell cycle, Western blot analysis for EMT marker proteins and MTA3 protein expression, calcium flux, and histone deacetylase (HDAC) activity were employed to investigate the impact of AgNPs on MCF-7 cells. The study also evaluated the effect of AgNPs on mitochondrial membrane potential to gauge their direct influence on mitochondria. Results indicated enhanced mobility of MCF-7 cells compared to control cells and their resistance to the cytotoxic effects of AgNPs. Treatment with AgNPs led to increased ROS production, while no significant impact on the cell cycle was observed. Instead, it altered the expression of the MTA3 and EMT marker proteins. Results imply that AgNPs change breast cancer cells' metabolism and activate a number of metastasis-related pathways by causing the formation of reactive oxygen species.72[85].

❖ **Cobalt**

In the context of clinical hyperthermia applications, researchers have investigated the potential of magnetic nanoparticles such as cobalt ferrite (CFNPs) for cancer treatment. These CFNPs,

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synthesized through thermal decomposition with the nonionic surfactant Triton-X100, feature hydrophilic polyethylene oxide chains that act as reducing agents for cobalt and iron precursors. High-resolution transmission electron microscopy revealed monodispersed nanoparticles measuring 10 nm in size. The study exposed triple-negative breast cancer cells (TNBC) to microwaves in the presence of varying CFNP concentrations (5 mg/mL to 40 mg/mL), resulting in increased cytotoxicity compared to CFNPs alone. A controlled thermal breakdown synthesis was employed to produce uniform CoFe2O4 nanoparticles, where higher temperatures led to reduced oxygen solubility, forming a smaller oxide layer during synthesis and enhancing particle reliability. Subsequent in vitro hyperthermia tests on TNBC cell lines and fibroblast cells utilized pure nanoparticles redispersed in physiological saline. 15 tilizingIn their study team was successful in creating CFNPs with an appropriate design, morphological structure, and content for hyperthermia treatment.73 [86].

- **Oxide**

Materials such as zinc oxide and tin oxide, known for their versatile physicochemical characteristics, offer promising solutions for addressing this problem. Zinc oxide nanoparticles (ZnO NPs) exhibit considerable potential in addressing the issue due to their adaptable properties. In contrast to pure ZnO NPs, they create SnO2-doped ZnO NPs/reduced graphene oxide nanocomposites (SnO2-ZnO/rGO NCs) with improved anticancer activity and biocompatibility. SnO2-ZnO/rGO NCs outperformed SnO2- ZnO NPs and pure ZnO NPs in terms of anticancer activity and biocompatibility. This research offered a fresh method for enhancing ZnO NPs' selectivity and anticancer properties. The synthesis of SnO2-ZnO/rGO NCs was accomplished by a straightforward hydrothermal process. The production of hexagonal wurtzite ZnO in a single phase was confirmed by XRD measurements.In ZnO NPs, SnO2 and rGO were distributed uniformly according to HRTEM and SEM mapping, which also revealed high-quality lattice fringes that were distortion-free. Our findings suggested a novel strategy for modifying the physicochemical properties of ZnO to enhance its selectivity and anticancer activity in human breast cancer cells.74 [87].

The aim of this investigation was to enhance the efficacy of ZnO/ZrO2/rGO nanocomposites (NCs) in combating cancer while preserving the integrity of healthy cells. Various analytical techniques, including transmission electron microscopy (TEM), scanning electron microscopy (SEM), energy dispersive X-ray spectroscopy (EDS), X-ray diffraction (XRD), photoluminescence (PL), and dynamic light scattering (DLS), were employed to validate the synthesis of pure ZnO nanoparticles (NPs), ZnO/ZrO2 NCs, and ZnO/ZrO2/rGO NCs. XRD spectra revealed two distinctive sets of diffraction peaks for ZnO/ZrO2/rGO NCs. Biologically, ZnO/ZrO2/rGO NCs demonstrated approximately 3.5 times greater anticancer efficacy in human lung cancer (A549) and breast cancer (MCF7) cells compared to ZnO NPs. A mechanistic exploration revealed that oxidative stress, as evidenced by increased intracellular reactive oxygen species levels and decreased glutathione levels, mediated the anticancer response of ZnO/ZrO2/rGO NCs. The findings of this study suggest that ZnO/ZrO2/rGO NCs, facilitated by ginger extract, could serve as a promising therapeutic agent for cancer treatment.75 [88].

Lipid based nanocarriers

Lipid-based delivery platforms stood out among these nanocarriers as one of the best possibilities for cancer therapy because they enhanced the therapeutic efficacy and safety profile of encapsulated medicines.

This research primarily focuses on discussing and elucidating the recent advancements in delivery systems designed for treating metastasis in breast cancer (BC). The emphasis is specifically on targeting prevalent metastatic locations in the bone, brain, and lungs. The study highlights the remarkable capability of curing BC metastasis through the use of liposomes and lipid-based nanoparticles (LNPs) for delivery, surpassing the effectiveness of systemic chemotherapy.76[89]. Various lipid-based nanoparticles, including liposomes, nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid nanocarriers (NLCs), and lipid-polymer hybrid nanoparticles (LPH-NPs), have been developed and extensively documented for cancer therapy.77[90]. LNPs, such as

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liposomes, exhibit therapeutic advantages compared to traditional methods and other nanoparticles, such as enhanced stability, increased loading capacity, reduced therapeutic dose and associated toxicity, and decreased drug resistance. Moreover, LNPs overcome physiological barriers, leading to greater therapeutic accumulation at the targeted site.

The lipids utilized in LNP production, such as liposomes, nanoemulsions, SLNs, NLCs, and LPH-NPs, were found to be non-toxic, biocompatible, and biodegradable with minimal immunogenicity. Lipids have been extensively investigated as nanocarriers for cancer-targeted drug delivery systems due to their ability to form nanostructures. Additionally, the physicochemical characteristics of lipids offer opportunities for customization in terms of particle size, morphology, entrapment efficiency, drug loading, and in vitro drug release profile, thereby enhancing the drug delivery system.78[91].

However, the study also revealed heightened cytotoxicity and potential metastatic activity of lipid-based formulations against human breast cancer cells, suggesting significant potential for pre-clinical and clinical translation. Another investigation highlighted the efficacy of combining Artemether (ART) and docosahexaenoic acid (DHA) as a novel strategy for breast cancer treatment. The study explored the potential of using DHA as a medication delivery platform for breast cancer cells in three different lipid nanocarriers (NC, NLC, and NE). The results indicated dose-dependent cytotoxicity in MDA-MB-231 and MCF-7 cells for all three formulations.insert additional information as neededAccording to the long-term effects of the nanocarriers containing ART/DHA, the combination may affect how breast cancer cells form colonies in addition to causing MCF-7 cells to undergo apoptosis and only mild necrosis. Our confocal and flow cytometry experiments demonstrated that this may be caused by the interaction of NC, NLC, and NE lipid nanocarriers within MDA-MB-231 and MCF-7 cells. To get around these issues, the usage of nanocarriers is being researched.79[92]. Researchers describe a novel class of hybrid nucleoside-lipid-based sorafenib-based nanoparticles. The solid lipid nanoparticles (SLNs) demonstrated negative or positive zeta potential values depending on the nucleoside-lipid charge. Sorafenib-loaded SLNs revealed by transmission electron microscopy contained 200 nm parallelepiped nanoparticles. Studies conducted on four different cell lines, including those from breast and liver malignancies, demonstrated that Sorafenib-based SLNs have stronger anticancer properties than the free drug. The potential of nucleoside-lipid-based SLNs as drug delivery systems is highlighted by these findings. This is the first instance of a trial that uses sorafenib to treat luminal B breast tumours and shows how effective the SLN strategy is. The findings presented here demonstrate the potential of nucleoside-lipid-based SLNs as drug delivery platforms. The biocompatible Nature that SLNs offer makes it possible to incorporate a wide range of medications and treat various tumour types while overcoming cancer cells' resistance mechanisms. Moreover, SLNs are able to cross biological barriers and promote the cellular uptake of the medications via modulating passive, active, and co-transport processes.80 [93].

To enhance the prolonged release and stability of drugs while utilizing non-toxic nanocarriers and improving bioavailability through pulmonary administration, a prior investigation aimed to formulate solid lipid nanoparticles (SLNs) loaded with NRG (a poorly water-soluble medication). The selection of the optimal solid lipid matrix for SLN creation was initially determined using a group contribution technique. NRG-SLNs were then produced through emulsification and low-temperature solidification, with an orthogonal experimental strategy employed for optimization. The results indicated that SLNs present a feasible pulmonary delivery approach for enhancing the bioavailability of water-insoluble drugs such as NRG.

The successful insertion of NRG into SLNs using the emulsification and low-temperature solidification method was further optimized through an L9 (34) orthogonal design, highlighting the potential of SLNs as a pulmonary delivery system for poorly water-soluble medications like NRG.[94]

Micelles

In a previous investigation, researchers created a unique medication by linking a drug called DOX to a substance known as TPGS2000. This specialized medication, referred to as TPGS2000-DOX, exhibits enhanced effectiveness in treating tumors due to its ability to release the drug directly within

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the tumor, resulting in improved treatment outcomes, reduced side effects, and increased difficulty for tumor cells to develop resistance to the drug. To produce this unique medication, they established a robust chemical connection between DOX and TPGS2000. TPGS2000-DOX is encapsulated within minuscule particles referred to as micelles, which possess a remarkable capacity for locating and homing in on tumors. In experiments, these micelles demonstrated their capability to deliver the medication precisely to the tumor site. This novel approach to drug delivery using nano-sized particles has potential applications in both disease treatment and diagnosis. It holds particular promise for breast cancer treatment due to its efficacy and selectivity in targeting breast cancer cells[82 [95].

For the encapsulation of res and coumarin 6, researchers have effectively produced and characterised a drug delivery system using Pluronic F127 and Vitamin E TPGS, resulting in a completely soluble drug formulation. The resultant nanoparticle had minimal absorption by immortalised healthy epithelial cells and was efficient at preferentially targeting aggressive forms of breast cancer. Furthermore, the nanoparticle significantly reduced the cell viability of breast cancer cells while having no discernible harmful effects on breast cells that had been immortalised. These findings imply that the suggested nanoparticle is a potentially effective platform for delivering medicines to breast cancer cells for both diagnostic and therapeutic purposes.83[96]. Recent research suggests that triple-negative breast cancer treatment with HTPMs (Halofuginone hydrobromide-loaded TPGS PMs) has a great deal of clinical promise. The thin- film ultrasonic technique was successful in creating HTPMs. The improved HTPM demonstrated better suppression of TNBCs than free HF and PTX in addition to having a small size with restricted dispersion, superior stability, and prolonged release behaviour. Additionally, by destroying mitochondria and boosting ROS production, HTPM caused the death of breast cancer cells. HTPM also showed good biocompatibility and significantly reduced in vivo tumour development in tumor-bearing animals.

The findings suggest that the use of thin-film hydration yielded successful creation of halofuginone (HF)-loaded TPGS polymeric micelles (HTPM), demonstrating promising therapeutic potential for triple-negative breast cancers (TNBCs).84 [97]. Intravenous administration of HTPM exhibited excellent anticancer effects on both subcutaneous xenografts and TNBC cells. The study further explored the therapeutic impact and mechanism of orally administered HTPM alone and in combination with surgical therapy in subcutaneous and orthotopic mouse models of TNBC. The as-prepared HTPM, characterized by smaller diameters and a uniform distribution, demonstrated remarkable stability and sustained release behavior in simulated gastrointestinal fluids. TPGS polymeric micelles not only enhanced intestinal absorption by preventing P-gp efflux but also significantly increased cellular permeability to HF. Oral administration of HTPM notably reduced gastrointestinal toxicity in subcutaneous tumor mouse models compared to HF. Additionally, gavage-administered HTPM effectively reduced lung metastasis of TNBC and enhanced the therapeutic impact of HF against residual tissues in TNBC orthotopic xenografts post-surgical resection. The results highlight the potential of HTPM as an oral anticancer treatment for TNBC.85 [98].

In a separate investigation, the current study evaluated the anticancer effects of an oral nanomicellar (NM) formulation of Honokiol against various TNBC cell lines. Cytotoxicity, clonogenic activity, and wound healing assays demonstrated the efficacy of the oral Honokiol NM formulation in inhibiting TNBC growth. Studies on the permeability of Caco-2 in vitro revealed Honokiol was more readily absorbed. It proves that using a nanomicellar formulation is a better option than using other techniques when using anticancer substances like HNK. Their nanomicellar formulation methods open up new channels for therapeutic administration ways to enhance the efficacy of orally active, secure anticancer medications.86 [99]. To improve the efficacy of docetaxel against triple-negative breast cancer (TNBC), a novel delivery method was devised using RGD-modified PEGylated lipid-core micelles. These micelles, designed to target TNBC tumors, were thoroughly characterized in terms of their morphology, size, zeta potential, encapsulation efficiency, release kinetics, and targeted effects. The anticancer properties of docetaxel-loaded nano-micelles were evaluated both in vitro using an MDA-MB-231 cell model and in vivo using an MDA-MB-231

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xenograft model. The innovative RGD-modified PEGylated Lipid-Core Micelle Delivery System significantly enhanced the anticancer effects of docetaxel while concurrently mitigating its adverse effects. This approach holds promise as a potential therapeutic strategy for the treatment of TNBC. To enhance the therapeutic effects of DTX on TNBC, they created a brand-new RGD-modified lipid micelle delivery method. RGD-DTX-straightforward M's preparation procedure made it possible to produce these formulations in large quantities. High encapsulation efficiency and sustained release properties in the produced RGD-DTX-M made it suitable for intravenous administration. According to the results of the pharmacokinetics study, RGD-DTX-M had a 3.2-times more absolute bioavailability when compared to DTX commercial injections, and it had a 5-times greater anticancer impact in mice with the MDA-MB-231 tumour. Its good safety was evidenced by preliminary safety results.[87,100]

b) **Nanobubbles**

The use of nanobubbles (NBs) that can target tumour cells in ultrasound (US) molecular imaging has enormous promise for more accurate diagnosis and treatment. However, the development of current targeted medicines is hampered by the absence of traditional biomarkers in TNBC. Thus, scientists created the first NBs based on TNBC cancer cell membrane (i.e., NBCCM) as a targeted diagnostic agent by taking advantage of the homotypic identification of cancer cells. A research aimed to create a microfluidic technique to create NBCCM based on the ability of cell membranes to self-assemble in aqueous solutions. Biomimetic bubbles enable for individualised treatment, which may provide the best possibilities for effective TNBC targeting when compared to traditional targeted UCA formulations. We believe that the cell membrane-based NBs shown in this work are just the beginning of the development of tailored UCAs with significant oncological potential. This strategy could be employed for a variety of diagnostic and therapeutic objectives, including the development of tailored drug delivery systems, immunomodulatory medicines, and cancer vaccines. [88,101] A separate investigation looks into whether the "nanobubbles" that lasers create around nanoparticles cause an immune response that can be used to treat cancer. In the cytoplasm of breast cancer cells, a single 1064 nm nanosecond laser pulse causes micron-sized bubbles to surround gold nanorods. Nanorod treatment and radiation caused cell death in some cells, but not in cells that had just been exposed to radiation. With simultaneous immunogenic cell death signalling and quick and highly specific tumour cell eradication, this treatment modality has promise as an immunotherapy combo approach. They found that nanosecond pulsed laser irradiation offered a quick and highly targeted method to eliminate tumour cells and trigger immunogenic cell death markers. [89,102]

In a previous article describes the development of a DNA vaccine delivery system using specifically designed chitosan-shelled nanobubbles (NBs) for the treatment of HER2 + breast cancer. Anti-CD1a antibodies have been added to the NBs to make them functional and target dendritic cells (DCs). The NB formulations are positive surface charged, have diameters of about 300 nm, and exhibit good physical stability for up to 6 months when stored at 4 °C. This study has successfully created chitosan-shelled NBs loaded with DNA vaccine and directed to DCs for the treatment of HER2 + breast cancer.

This kind of NBs has the capacity to load DNA with good encapsulation efficiency and release it over a lengthy period of time under tightly controlled kinetics. It demonstrated the ability to very selectively transfect DCs and trigger their activation in both human and mouse cell lines.[90,103]

a) **Nano bins**

To enhance the fidelity of simulating the triple-negative breast cancer (TNBC) tumor microenvironment in vitro, this recent study introduces a distinctive 3D co-culture spheroid model (3D TNBC). This model integrates color-coded murine tumor tissue analogs (TTA) by combining tumor cells, endothelial cells, and fibroblasts. The implanted TTA in nude mice demonstrates heightened growth and rapid metastasis to distant locations, establishing a mechanistic link between in vitro and in vivo outcomes. This approach enables the evaluation of both traditional and innovative combinational cancer nanotherapies. [91,104]

Recent findings highlight an elevated expression of stromal galectin-1 in clinical TNBC samples. Ongoing research explores stromal targeting of radiation-induced galectin-1 using anginex-conjugated arsenic-cisplatin-loaded liposomes. Employing a TNBC model with orthotopic tumors

derived from 3D TTA, consisting of tumor cells, endothelial cells, and fibroblasts, the study demonstrates the prevention of tumor growth and metastasis through a multimodal nanotherapeutic strategy. The outcomes illustrate the utilization of therapeutically relevant radiation doses to facilitate concurrent receptor-mediated enhanced chemotherapeutic administration, while minimizing systemic toxicity. [92,105,106,107,108].

Conclusion and Discussion

Breast cancer, especially TNBC, is becoming the focus of current research due to a lack of suitable TNBC therapy compared to other hormone-positive breast cancers. Researchers discovered that a thorough understanding of TNBC pathophysiology is the most important factor in producing better-functioning NPs. Tumor target-based techniques and controlled payload release are deemed essential for addressing any sort of malignancy. Polymeric nanocarriers stand out as a viable technique for TNBC therapy due to their physiochemical features and multifunctional nature. There are now combinations of chemotherapy with novel targeted drugs and molecular gene therapy that can help patients survive longer. To enhance clinical applicability in large populations, we know that innovative therapeutic techniques, such as molecular gene therapy, are necessary.

In this review, we discussed recent advances in breast cancer diagnosis and treatment using nanocarrier's dendrimers, Nano emulsion, Carbon Nanotubes, Nanoparticles like Polymeric, Magnetic nanoparticles, Metallic Polymersome (Platinum and Palladium, Gold, Copper, Silver, Cobalt Doped, Tin Oxide), Lipid-based nanocarriers, Micelles, Nano bins, and Nanobubbles. Nanoparticles provide sophisticated tumor targeting strategies with increased efficacy and less toxicity. Several nanoparticle compositions are currently being used in therapeutic settings. Continuing efforts by researchers, doctors, and other medical workers in the field of nanotechnology will develop a new platform for nanoparticles on a constant basis. In the near future, nanotechnology will not only have a greater use in cancer, but it will also improve the discipline of medicine.

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