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Nano Formulation Devices Technology for Targeting Breast Cancer Chemotherapy

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ABSTRACT
Cancer, a multifaceted illness, entails unchecked and atypical cell growth, resulting in tumours, invasion, and spreading. The majority of antineoplastic medications are neither specific nor selective for malignant cells. Therefore, they exert a significant toxic impact on normal healthy cells. This typically relates to the dosage and administration schedule (frequency of administration) for any cancer treatments. Breast carcinoma poses a significant health issue for women globally. Therefore, the primary emphasis of cancer treatment must prioritize greater selectivity of chemotherapeutic agents towards the neoplastic cells while preventing their effect on the normal healthy cells. Nanocarriers for drugs are now being utilized to enhance traditional cancer chemotherapy. Numerous nanoscale active ingredient molecule carriers are designed to deliver the medication to the specific location to prevent dose-related toxicity, while improving drug effectiveness, biocompatibility, and stability. Nanoformulations enhance the duration that active pharmaceutical ingredients stay in the bloodstream, resulting in the build-up of medicine within cancer cells because of their "permeable blood vessels." Nanoformulations can effectively reach cells or tissues through mechanisms of "active or passive targeting". The passive targeting mechanism affects the tumour environment, enabling the vesicular flexibility of nanodevices to penetrate neoplastic cells and accumulate within them due to the "enhanced permeability and retention effect." The nanoparticle formulations for cancer treatment could be enhanced by incorporating targeted ligands linked to the molecules on the nanodevice surfaces, enabling precise drug delivery to cancerous cells.

Keywords: Antineoplastic Medications, Active or Passive Targeting, Nanodevices, Enhanced Permeability and Retention Effect

Introduction

Cancer begins due to the irregular growth and division of cells, mainly caused by mutations in regulatory genes. The genes that play a role in the development and progression of cancer fall into three categories: oncogenes, proto-oncogenes, and neoplastic cells suppressor genes. Proto-oncogenes are standard genes that do not cause health issues [1]. However, when these proto-oncogenes undergo mutations, they transform into oncogenes that generate various onco-proteins, resulting in disruptions in the overall cell cycle and the development of cancer. Oncoproteins alter cellular balance, influencing cell cycle regulation, programmed cell death, and genome integrity. By modifying signalling pathways, they either encourage uncontrolled cell proliferation or initiate programmed cell death [2]. Additionally, their impact reaches the disruption of processes that protect genomic integrity, which speeds up mutagenesis and increases the likelihood of cancerous change. The proteins produced by malignant cells suppressor genes, also known as molecular switches, play a role in DNA repair processes and the removal of damaged cells. Their mutation likewise leads to irregularities in cell division and growth. Mutations in essential genes that are part of cell cycle regulation pathways result. The beginning of cancer formation [3]. The initiation process involves effective DNA repair mechanisms, allowing initiated cells to survive as they advance toward preneoplastic focal lesion formation. The cells of the preneoplastic focal lesion exhibit ongoing proliferation because of the steady availability of factors that encourage cancer progression, ultimately resulting in metastasis [4].

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Breast cancer is among the most frequently diagnosed cancers and is the primary cause of cancer-related deaths in women globally. The major challenges of traditional chemotherapy are significant side effects and quick onset of drug resistance in neoplastic cells. Since most chemotherapeutic medicament lacks selectivity for cancer cells, a key objective in enhancing the efficacy and tolerability of chemotherapy is the targeted delivery of the therapeutic agent to cancerous tissues [5].

A key objective to enhance the effectiveness and tolerability of chemotherapy is the targeted delivery of the therapeutic agent to cancer tissues while concurrently reducing harm to healthy organs. Molecular investigations revealed that the expression of mutated genes significantly regulates the development and progression of breast cancer [6]. To tackle this challenge, various drug and gene delivery systems have been created, including viral vectors and non-viral options like liposomes, polymers, and inorganic nanoparticles. At present, the main approach for treating breast cancer cells is surgery, followed by the use of chemotherapy and radiotherapy [7]. Nonetheless, these later interventions frequently fail to adequately address breast cancer because of their adverse effects and damage to healthy tissues. Currently, various nanoparticles are being created to specifically attack BC cells while sparing the adjacent healthy tissues. Investigation in nanotechnology for cancer treatment goes beyond traditional drug delivery, exploring the creation of new therapies enabled by the unique properties of nanomaterials [8]. Moreover, nanotechnology has effectively tackled the significant problem of unintended and nonspecific harm to body tissues caused by traditional treatment methods. A notable benefit is the application of multifunctional nanocarriers, which take advantage of the differences between tumor and normal tissues to selectively transport therapeutic drugs, enhancing drug permeability and retention [9]. Nanoparticles are large enough to hold many small molecules while still being relatively small compared to cells. The comparatively extensive surface area of nanoparticles can also be modified with ligands like DNA or RNA strands, aptamers, peptides, and antibodies. Additionally, since conventional drug delivery techniques subject medications to the body's metabolic processes, erratic pharmacokinetics may occur. In this instance, the administered dose exceeds what is required, potentially resulting in heightened drug toxicity [10].

In this situation, the administered dose exceeds what is required, potentially resulting in heightened drug toxicity. Breast cancer is a varied disease whose biological features can be categorized based on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2). Nanoformulations are therapeutic agents encased in nanoparticles [11]. Nanoformulations offer the benefit of being able to target tumors actively or passively for drug delivery, while also allowing for sustained or controlled release directly at the tumour tissue location. Nanoparticles consist of polymer nanoparticles, liposomes, and micelles, distinguished by their ability to encapsulate drugs with limited solubility, enhance drug bioavailability, target drug delivery, modify drug release, and enable simultaneous treatment in cancer diagnosis [12].

Therapeutic Benefits of Nanoparticles in Breast Cancer Therapy

The issues created by traditional therapies, resulting in random harm to bodily tissues, have been successfully tackled by the swift progress in nanotechnology. This technology offers unique benefits by improving the effectiveness of radiation treatment and drugs while reducing adverse effects [13]. Multifunctional The issues created by traditional treatments, which harm body tissues indiscriminately, have been successfully tackled by the swift progress in nanotechnology. This technology offers clear benefits by improving the effectiveness of radiation treatment and drugs while reducing side effects. Multifunctional nanocarriers exploit the disparities between tumor and healthy tissue, enabling the targeted delivery of therapeutic drugs and enhancing drug permeability and retention [14]. Additionally, the distinct physical and chemical properties of the tumor microenvironment (TME), such as low oxygen levels, mild acidity, altered pH, atypical temperature variation, and overexpressed enzymes and proteins, can be utilized to regulate the release rate of drugs from nanocarriers. Nanocarriers exploit the disparities between tumor and healthy tissue, enabling targeted delivery of therapeutic agents while enhancing drug absorption and retention [15].

Additionally, the distinctive physical and chemical properties of the tumor microenvironment (TME), such as hypoxia, mild acidity, reduced pH, atypical temperature gradients, and overproduced proteins and enzymes, can be utilized to regulate the drug release rate from nanocarriers [16]. Nanomaterials are generally classified into two primary subcategories: nanocrystalline and nanostructured. In the classification of nanostructured materials, lipid-based nanoparticles, as well as nonpolymer and polymer-based nanoparticles, belong to this group. Polymer-derived nanoparticles include dendrimers, micelles, nanogels, protein nanoparticles, and drug conjugates. Nonpolymeric nanoparticles consist of silica nanoparticles, metallic nanoparticles, quantum dots, carbon nanotubes, and nanodiamonds [17]. The nanoparticles that have received clinical approval for therapeutic applications mainly comprise polymer- or lipid-based materials. When choosing therapeutic nanoparticles, important factors to take into account involve absorption, circulation, secretion, engagement with cells and substances, alteration of the immune response, extended lifespan, and general effectiveness. The mechanisms referred to in this section stem from the fundamental properties of nanoparticles [18].

Passive targeting

In healthy tissue, close endothelial junctions inhibit the entry of suitably sized nanoparticles into blood vessels. Nonetheless, unusual neovascularization at the tumour location shows an excessive permeability condition, enabling the nanoparticles to cross the vascular endothelium openings and access the tumor stroma, thereby promoting passive targeting. This occurrence is referred to as the enhanced permeability and retention (EPR) effect [19]. Utilizing EPR, nanocarriers can differentiate between healthy and tumour tissues, resulting in increased concentration of localized nanoparticles in tumours and thereby improving treatment effectiveness against breast cancer. At the same time, it was noted that albumin nanoparticles demonstrate passive targeting, primarily linked to the enhanced EPR effect as

their main targeting mechanism [20]. Additionally, the albumin nanoparticles attach to Gp60 receptors located on the surface of cancer cells. Gp60 additionally interacts with an intracellular protein-1, triggering membrane invagination to form transcytosis vesicles that enable albumin nanoparticles to traverse the endothelial cell. Albumin nanoparticles attach to cysteine-rich acidic secretory protein (SPARC) that is highly expressed in many tumour cells within the tumor stroma, resulting in the build-up of albumin nanoparticles in the tumour context and damaged tissues [21]. Albumin particles demonstrate effective targeting via multiple routes. Regulatory agencies like the U.S. Food and Drug Administration and the European Medicines Agency have authorized the albumin-bound paclitaxel (nab-P) nanoparticle formulation (Abraxane®) for managing metastatic breast cancer. The pairing of paclitaxel with albumin nanoparticles enhanced anti-cancer efficacy and lowered toxicity [22].

Active Targeting

Active targeting primarily focuses on receptors that are abundantly present in malignant cells. Nanoformulations alter the nanoparticle surfaces through covalent bonding, electrostatic adsorption, or surface coating techniques, utilizing folic acid (FA), transferrin, biotin, and other ligands as targeting agents for precise tumour targeting [23].

The excessive expression of the FA receptor on breast cancer cells, combined with its strong affinity for the ligand and specific binding capacity, makes FA an appropriate surface-associated ligand for targeted cancer treatment. In vitro research has demonstrated that the formula is very efficient and can effectively target and transport drugs in a precise way [24]. Tf plasma glycoprotein serves as an iron carrier that aims to specifically target the overproduced transferrin receptor (TfR1) found on tumour cell surfaces to treat Doxorubicin (DOX) sensitive as well as drug-resistant tumour. Experiments showed effective accumulation in a DOX-resistant cell line MDA-MB-231(R) xenograft mouse model with low toxicity to healthy tissues [25].

Furthermore, the development of breast cancer is controlled by receptors, and targeted therapy actively employs certain antibodies to target and block these receptors. Currently, the primary targets in breast cancer therapy include HER-2, heparin binding epidermal growth factor-like growth factor (HB EGF), epidermal growth factor receptor (EGFR), insulin-like growth factor 1 receptor (IGF-IR), vascular endothelial growth factor receptor (VEGFR), estrogen receptor, cyclooxygenase-2 (COX-2), etc [26]. Receptors' growth can be directly blocked by antibodies, which may also be linked to anti-cancer drugs for precise delivery within the body. This method has been effectively utilized for trastuzumab emtansine (T-DM1, Kadcyla®), which has obtained marketing authorization

Therapy with Dual Targeting

Certain medications enhance the alteration of ligands that target metastasis sites to create double-targeted nanomaterials, which are then employed to address subsequent breast cancer metastasis. Researchers employed dNP2 and folic acid (FA) modified liposomes to focus on brain metastases in breast cancer [27]. The dNP2 peptide was integrated into liposomes to improve their targeting of cancer cells and to boost BBB metastasis/cell absorption. In vivo analysis using a BALB/c mouse model with 4T1 cells revealed greater accumulation of double-targeted liposomes in the brain than other formulations. Moreover, following treatment with these liposomes, the advancement of tumors was significantly inhibited, and the lifespan of mice was extended [28]. Ke et al. created liposomes modified with aspartic acid (Asp8) and FA. Asp8 possesses a negative charge because of carboxylic acid ligands, allowing it to chelate calcium ions on the surface of hydroxyapatite (HA), a mineral unique to bone tissue. Thus, it can aim at cancer cells that have spread into the bone structure [29].

Nano Formulation Technologies in Cancer Treatment

Recent developments in nanotechnology offer hopeful approaches to avoid the unintentional damage to healthy tissues caused by traditional cancer treatments, including chemotherapy, radiotherapy, and immunotherapy [30]. The unique advantages of nanotechnology focus on enhancing the efficacy of drug and radiation treatments while reducing negative side effects. Multifunctional nanocarriers, for example, can take advantage of the differences between tumor and normal tissues to enhance drug delivery and retention selectively. In addition, the tumor microenvironment (TME) displays various physical and chemical traits, including irregular temperature gradients, reductive circumstances, slight acidity, hypoxia, and an overexpression of proteins and enzymes [31]. Utilizing these characteristics can facilitate the regulated release of medications from nanocarriers, enhancing the possibilities for precise and effective cancer therapies (Figure 1). Due to the swift progress of nanotechnology in recent decades, numerous nanomaterials have been created. Nonetheless, a restricted number of nanoparticulate systems are suitable for biomedical use, with an even smaller fraction satisfying the strict criteria established by the US FDA (United States Food and Drug Administration) for clinical purposes [32]. The application of engineered nanoparticles (NPs) for specific cancer treatment, such as breast cancer, is an expanding area of study. The aim is to enhance treatment effectiveness, reduce side effects, and increase the overall quality of life for patients. These NPs can be tailored to attach selectively to cancer cells, thereby guaranteeing that therapeutic agents reach the intended site [33].

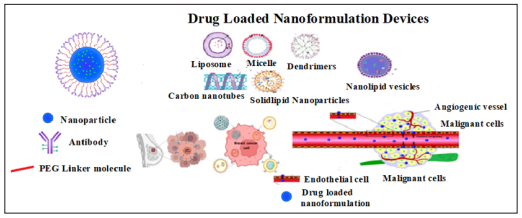

Figure 1: Nanoformulation devices in breast cancer chemotherapy

Healing Attributes of Nanoparticles in Breast Cancer Therapy

The issues resulting from traditional therapies, which harm body tissues indiscriminately, have been successfully tackled by the swift progress in nanotechnology. This technology offers unique benefits by improving the effectiveness of radiation treatment and drugs while reducing adverse effects [34]. Multifunctional The issues presented by traditional treatments, which indiscriminately harm bodily tissues, have been

adeptly tackled by the swift progress in nanotechnology. This technology offers unique benefits by improving the effectiveness of radiation treatment and drugs while reducing side effects [35]. Multifunctional nanocarriers exploit the variations between neoplastic cells and normal tissues, enabling the targeted delivery of therapeutic active ingredient(s) and enhancing antineoplastic medicament retention and permeability [36]. Additionally, the distinctive physical and chemical properties of the malignant cells microenvironment (TME), such as hypoxia, mild acidity, reduced pH, atypical temperature gradients, and overexpressed proteins and enzymes, can be utilized to regulate the release rate of antineoplastic medicament(s) from nanocarriers. Nanodevices take advantage of the variations between neoplastic cells and normal tissues, enabling targeted delivery of therapeutic agents and enhancing active neoplastic component permeability and retention [37]. Additionally, the distinctive physical and chemical properties of the malignant cells microenvironment (TME), such as hypoxia, slight acidity, reduced pH, atypical temperature gradient, and overexpressed proteins and enzymes, can be utilized to regulate the release rate of chemotherapeutic medicament from nanocarriers. Nanomaterials are generally classified into two primary subcategories: nanocrystalline and nanostructured. In the classification of nanostructured materials, lipid-based nanoparticles are included alongside both polymer and nonpolymer-based nanoparticles [38]. Polymer-derived nanoparticles include dendrimers, micelles, nanogels, protein nanoparticles, and active neoplastic molecule conjugates. Nonpolymeric nanoparticles consist of silica nanoparticles, metallic nanoparticles, quantum dots, carbon nanotubes, and nanodiamonds. Besides polymer-based nanostructured particles, nonpolymers, or lipids, particular therapeutic applications also utilize nanocrystalline particles created through the crystallization of pharmaceutical compounds [39].

Breast Cancer Therapy Through Medicament Delivery Using Triggerable Liposomes

The on-demand delivery of encapsulated medications from liposomes has surfaced as a recent innovation. The improvement of this technology through the engineering of triggerable liposomes draws significant interest [40]. Different triggering modalities were investigated for prompting an immediate medicament release from liposomes and categorized into internal and external triggers. Internal triggers relate to the specific physiological properties of the tumor microenvironment and encompass changes in pH and the influence of enzymes. External triggering sources include heat, light, ultrasound, and magnetic fields [41]. These triggering modalities have been extensively utilized in liposome technology for breast cancer therapy in preclinical studies (Table 1). Although highly significant, the triggering mechanisms are not the main emphasis of this article since they were thoroughly reviewed, analyzed, and interpreted recently [42].

Additionally, nanolipid vesicles conjugated with antibodies and loaded with anticancer medications demonstrated significant cellular uptake in MCF-7 cells and MDA MB-453 cells. This formulation was created for active targeting by binding the specific antibody (FITC anti-human CD 340 (erbB2/HER-2)) to the linker molecules (PE) found on the surface of the phospholipid bilayer [43]. The antibody-conjugated nanoliposome demonstrated a quicker and more efficient uptake by MCF-7 (estrogen receptor-positive) cancer cells than the MDA-MB-453 (estrogen receptor-negative) cancer cells, indicating selective uptake and implying potential success in targeting breast cancer cells [44]. FACS analysis revealed that the experimental formulation led to an increase in apoptotic and preapoptotic cell numbers. This indicates that using liposomal drug therapy would be more advantageous for managing the disease than treatment with the free drug [45]. In the future, a study can be conducted on the preferential cellular uptake for various breast cancer cell lines and their quantitative comparison. Additional research is needed to explore the effectiveness of the antibody conjugated liposome in breast cancer animal models in vivo. Nevertheless, all experimental findings from this study indicate that the antibody-tagged modified nanolipid vesicles may be advantageous for breast cancer chemotherapy [46].

Table 1: Different types of nanoformulations in targeting breast tumor cells and metastatic sites

Nanoformulation devices	Therapeutic Agents
Abraxane	albumin-bound paclitaxel nanoparticles
Doxil	Liposomal doxorubicin
MM 302	Liposomal doxorubicin with HER-2 targeting antibody
CAL AA-01	Si-RNA containing cyclodextrin nanoparticles
Genexol-PM	Polymeric micellar paclitaxel
CT-2106	Polymeric nanoparticle paclitaxel
Onivyde	Cirinotecan liposomal injection
BIND-014	Docetaxel loaded polymeric nanoparticles
Cellax	Docetaxel acetylated carboxymethyl cellulose linked with PEG nanoparticles
Liposomes decorated with lapidated cathepsin B inhibitor	NS 629

PEGylated Nanoliposomes for the Treatment of Breast Cancer:

Numerous preclinical investigations have demonstrated that anticancer drugs encapsulated in PEGylated nanoliposomes are promising nanotherapeutics for the treatment of breast carcinoma. Mirzavi et al. developed PEGylated nanoliposomes containing combretastatin A4 (CA4) made from hydrogenated soy phosphatidylcholine (HSPC), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethyleneglycol)2000] (DSPE-mPEG2000), and cholesterol for the treatment of breast cancer [47]. The transmission electron microscopy (TEM) and dynamic light scattering (DLS) studies of HSPC/DSPE-mPEG2000/Cholesterol/CA4 nanoliposomes revealed an average particle size ranging from 100 to 150 nm, exhibiting a negative surface charge and a PDI of less than 0.3, indicating that the sizes of these PEGylated nanoliposomes were uniformly distributed [48]. In vitro drug release assays under acidic conditions (pH 5.5 and 6.5, simulating tumor microenvironments)

and physiological conditions (pH 7.4, 37 ◦C) showed a pH-responsive release of CA4 from nanoliposomes, with elevated CA4 levels released at pH 5.5 and pH 6.5 compared to pH 7.4, suggesting that CA4-encapsulated nanoliposomes may exhibit greater cytotoxicity towards cancer cells than towards normal cells [49]. In vivo assessments utilizing the 4T1 xenograft BALB/c mouse model indicated that CA4 encapsulated nanoliposomes began to proliferate at the tumor location 3 hours post-injection, reaching peak accumulation in the tumor at 24 hours. These in vivo investigations additionally showed that HSPC/DSPE-mPEG2000/Cholesterol/CA4 nanoliposomes markedly decrease tumor growth in contrast to free CA4 without notable weight loss in the mice, indicating remarkable antitumor effectiveness against breast cancer without adverse effects [50].

PEGylation refers to the covalent attachment of PEG to nanocarriers, including nanoliposomes, dendrimers, micelles, lipid nanoparticles, or biomolecules, such as therapeutic proteins. PEGylation was primarily aimed at improving the pharmacokinetic characteristics of the PEGylated products and, as a result, enhancing the therapeutic efficacy of therapeutic proteins [51]. PEGylation was primarily aimed at improving the pharmacokinetic characteristics of the PEGylated products and thereby enhancing their therapeutic efficacy. PEGylated nanoliposomes enhance drug loading capacity by nearly 90%. PEGylated technology represents a hopeful drug delivery method, as it successfully transports both hydrophobic and hydrophilic bioactive compounds. PEG plays a crucial role in various nanoparticles as it readily dissolves in water, aids in regulating drug release rates, and remains stable in the bloodstream. PEGylated nanoliposomes reduce the number of encapsulated substances that escape. From now on, PEGylated nanoliposomes not only improve the bioavailability of the enclosed drug but also offer superior targeting of cancer cells [52].

Gene Therapy for Breast Cancer Using Liposome Technology

Every subtype of breast cancer linked to gene mutations led to specific cells in the breast becoming abnormal. Gene therapy represents a hopeful approach for addressing breast cancer subtypes with unique genetic changes, particularly for triple-negative breast cancers that cannot be effectively treated by targeted therapies due to the absence of receptors [53]. Cationic liposomes serve as promising gene delivery systems that can naturally associate with negatively charged DNA. Liposome bilayers can shield complexed nucleic acids from degradation by cells and neutralization by antibodies (Figure 1). Moreover, the positive charge of cationic liposomes enhances their interaction with the negatively charged cell membrane through endocytosis, leading to effective cellular uptake and release of contents into the cytoplasm [54]. The method for cancer gene therapy involves encapsulating plasmids and oligonucleotides within cationic liposomes. The CRISPR/Cas9 system, recognized as the most promising gene-editing technology for cancer gene therapy, will be examined separately [55].

Micelles

Unlike liposomes, which are bi-layer systems composed of phospholipid units, micelles are single-layer amphiphilic self-assembly structures made from repetitive units of surfactant molecules [56]. At low concentrations, surfactant molecules remain individual; however, as the concentration rises, they cluster together to create micelles, within a specific concentration range known as the critical micelle concentration (CMC). Micelles can host hydrophobic substances like TAM in their centers, while the hydrophilic outer layer shields them from degradation by the surrounding environment. Micelles, typically measuring 20-80 nm, are small enough to easily infiltrate the leaky blood vessels around tumors and remain there longer due to the EPR effect [57]. Although micelles show significant progress in TAM delivery, they possess a smaller drug-loading capacity and reduced stability compared to liposomes, owing to the reversible nature of their monomer components. Micelles typically exhibit lower toxicity and can be more readily removed from the body via renal filtration. Additionally, the water solubility of hydrophobic medications can be enhanced by as much as 500 times when they are enclosed within polymeric micelles. Gao et al. (2002) created TAM-loaded micelles using PEG 5000 modified with distearoyl-phosphatidylethanolamine (PEG5000-PE) to improve the tumour delivery of TAM [58].

These micelles could incorporate as much as 20 wt % of TAMS, showing enhanced drug accumulation in C57BL/6J tumor-bearing mice, particularly via tail vein injection. A different TAM-loaded micellar system was created using poly (lactic-co-glycolic acid) PLGA-PEG diblock copolymers, successfully increasing the bioavailability of TAM in the epidermis to 3.5 times that of native TAM [59]. The system's antitumor effectiveness against MCF-7 cell lines was also notably improved. Recently, new nanosized self-assembled core-shell structured micelles have been created from low molecular weight carboxymethyl chitosan and tocopherol succinate (TS) using a novel co-solvent evaporation method. The system reached a maximum TAM loading of 8.08 ± 0.98%. The system's stability was confirmed through in vitro release tests in simulated gastric and intestinal fluids, revealing a pH-dependent release pattern. In vivo studies also showed oral absorption, indicating a 1.9-fold rise in bioavailability when measured against free drug molecules. A new micellar TAM system based on palmitic acid and chitosan co-polymers was recently developed and assessed [60].

Nano Formulation Theragnostic

Numerous techniques are employed to identify breast cancer, including optical fluorescence imaging (FLI), photoacoustic imaging (PAI), computed tomography (CT), magnetic resonance imaging (MRI), and various other imaging methods [61]. These patterns can successfully identify tumors and other irregularities in the breast, enabling swift and efficient treatment to eliminate tumors and prevent metastasis [62]. Present studies mainly concentrate on theranostics, which entails observing treatment outcomes in real time by monitoring the medications utilized for cancer therapy. Theranostics offers individualized care to patients and enables prompt modifications to treatment [63].

Single Mode

By integrating imaging techniques like MRI, FIL, ultrasound, etc., with therapeutic medications, a hybrid approach of single-mode detection and treatment is created. Huang Peng's research team produced spherical nanoparticles (GOx-MnCaP NPs) through an in-situ bionic mineralization technique using manganese-doped calcium phosphate, subsequently loading DOX to create the GoX-MnCAP-DOX nanocomplex [64]. On

one side, Mn2+ facilitates a Fenton-like reaction that produces extremely harmful hydroxyl radicals for chemokinetic treatment. Conversely, emitted paramagnetic Mn2+ could be employed for MRI surveillance during therapy to accomplish the fusion of diagnosis and treatment. Additionally, Priyatosh et al. created stearic-g-polyethyleneimine acid amphiphilic nanomicelles modified with folic acid-based carbon dots (CDs) to specifically transport the anticancer medication DOX to triple-negative breast cancer cells, while also enabling bio-imaging. In vivo fluorescence imaging was performed with microspheres utilizing carbon quantum dots, a fluorescent carbon nanomaterial [65]. At the same time, this amphiphilic micelle demonstrated ideal release in the acidic tumour microenvironment and selectively targeted breast cancer cells via folic acid-mediated interactions. In experiments with MDA MB-231 breast cancer cells, the anticancer effectiveness of the DOX was enhanced by 250 times [66].

Bimodal

Some research also merges dual-modality imaging with treatment to enhance the shortcomings of single-modality. In recent times, NIR therapy has been widely employed in the treatment of tumors. Numerous studies integrate photothermal therapy with diagnostic techniques, employing certain materials capable of photothermal conversion to merge photothermal therapy with optical imaging [67]. However, optical imaging is constrained by variables like distance, so dual-mode imaging is employed to enhance the precision and accessibility of diagnosis. Researchers created a small molecule albumin nanosystem IR780@BSA@SPIO by encapsulating the formamide dye IR780 with superparamagnetic iron oxide (SPIO) via non-covalent interactions. IR780@BSA@SPIO merges IR-II with dual-mode MRI imaging, enzymatic catalysis, and photothermal conversion to significantly enhance the efficacy and precision of treatment [68]. Using imaging, the nanosystem can accurately identify cancer and direct photothermal treatment. The tumor proliferation's experimental irradiation with the IR780 laser led to a marked inhibition, demonstrating a remarkable photothermal treatment effect. Furthermore, the nanosystem activates the immune system and successfully prevents the progression of metastatic triple-negative breast tumors [69]. Moreover, Dongdong et al. created HER2-DOX SPIOs@PLGA@Au nanoparticles for the specific therapy of HER2-positive breast cancer. This particle facilitated dual-modal imaging of MRI and PA, employing gold to enhance photothermal and anti-cancer properties [70].

Multimodal

Every imaging method has its drawbacks, like MRI that offers high resolution but lacks sensitivity, and optical techniques that have restricted tissue penetration. The integration of various imaging techniques allows these applications to enhance each other [71]. Consequently, numerous studies integrate the therapy with three or more imaging detection modalities to enhance the treatment's effectiveness. In a research project, the writers described the creation of gold quantum clusters (AuQCs) utilizing alpha-lactalbumin (alpha-La), which is a globular metal protein [72]. As a multimodal imaging tool, AuQCs allow for accurate determination of tumor depth via CT or MRI and enable range imaging of localized tumors through Stokes large offset under visible excitation and NIR fluorescence emission, thus providing high-precision surgical vision during the ideal imaging window [73]. The results of the experiment indicated that after tail transfusions were administered to xenogeneic mice with MDA-MB-231 tumors, the tumors were easily identifiable within 30 minutes post-injection and remained distinguishable for as long as 168 hours [74]. Additionally, they showed that AuQCs can induce the suppression of the MAPK and PI3K–AKT pathways, exhibiting a strong local anti-tumor therapeutic effect [75].

Conclusion

Scientists have identified considerable advancements in the comprehension of cancer biology, resulting in the awareness of the varied characteristics of breast cancer. Biomarkers are essential for differentiating cancer types and detecting cellular irregularities that promote cancer progression. Nonetheless, in spite of this advancement, chemotherapy remains the main treatment for breast cancer because metastatic cells are resistant to therapies. Therapeutics based on nanomaterials have been created and investigated to ease and minimize the side effects linked to chemotherapy. Conventional medicament delivery systems have demonstrated shortcomings in targeted treatment, frequently resulting in decreased effectiveness. Conversely, nano formulation incorporated antineoplastic active pharmaceutical ingredient provide advantages such as surface alteration, precise delivery, and improved effectiveness. Employing nanodevices for targeted drug delivery enhances treatment effectiveness and allows for the incorporation of molecular biomarkers for accurate identification in breast carcinoma and their various subtypes. Furthermore, future assessments should consider the bioaccumulation of nano formulation post-drug release, location-specific interactions between nanoparticles and medicament molecules, potential physicochemical reactions occurring as nanodevices traverse different organs before arriving at target sites, and the self-transformation or self-digestion of specific nanodevices to improve the effectiveness of breast malignanacy recognition and recovery.

The application of nanoparticles for precise cancer treatment shows significant potential, yet many issues need to be resolved. These comprise the possible toxicity of nanoparticles, the challenges in managing medicament release, and the immune system's potential elimination of nanodevices. Nonetheless, due to continuous research and innovation, it is expected that adenocarcinoma treatments utilizing nano formulations will play a significant role in oncology moving forward. In summary, engineered nano structed devices present a promising and novel strategy for targeted breast malignancy treatment, potentially leading to significant improvements in patient outcomes.

Ultimately, it is important to highlight that breast carcinoma becomes the most lethal and challenging to manage once metastasis takes place. Breast malignancy often metastasizes to the bone, lung, liver, and brain, but these locations are not readily accessible to most anticancer therapies, including nano formulations. Robust collaboration with specialists in pharmacokinetics, toxicology, immunology, and oncology is anticipated to be crucial for future advancements in breast cancer nanomedicine.

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