

ROLE OF HERBAL NANOTECHNOLOGY IN TRIPLE NEGATIVE BREAST CANCER

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Abstract

Triple negative breast cancer (TNBC) is a malignant breast cancer subtype that is prone to progression, with high associated metastasis and five-year mortality rates and an overall poor prognosis. Chemotherapy is usually administered to treat TNBC without additional targeted therapies. Novel nanomaterials have a variety of excellent physical and chemical properties and biological functions (including targeting specificity), and contrast agents and drug delivery vectors based on nanotechnology are progressing towards a more accurate and targeted direction. This review discusses the mechanisms of action and prospects for the use of nanotechnology in the treatment of TNBC, thus providing potential new strategies for the diagnosis and treatment of TNBC.

Keywords: Triple-negative breast cancer, herbal nanotechnology, phytonanomedicine, targeted drug Delivery, natural compounds, nanoparticles

Introduction

Cancer is a major public health problem worldwide and the second leading cause of death in the United States. Cancer mortality rates have been rising throughout most of the 20th and 21st centuries, with 1,898,160 new cancer cases and 608,570 cancer deaths expected in the

United States as of 2021 . From 2010 to 2016, the five-year overall survival rate for all diagnosed cancers in the United States was 67% (68% for Caucasians and 63% for African Americans). Prostate cancer (98%), melanoma (93%) and female breast cancer (90%) had the highest associated survival rates, while pancreatic cancer (10%), liver cancer (20%), esophageal cancer (20%) and lung cancer (21%) had the lowest survival rates .

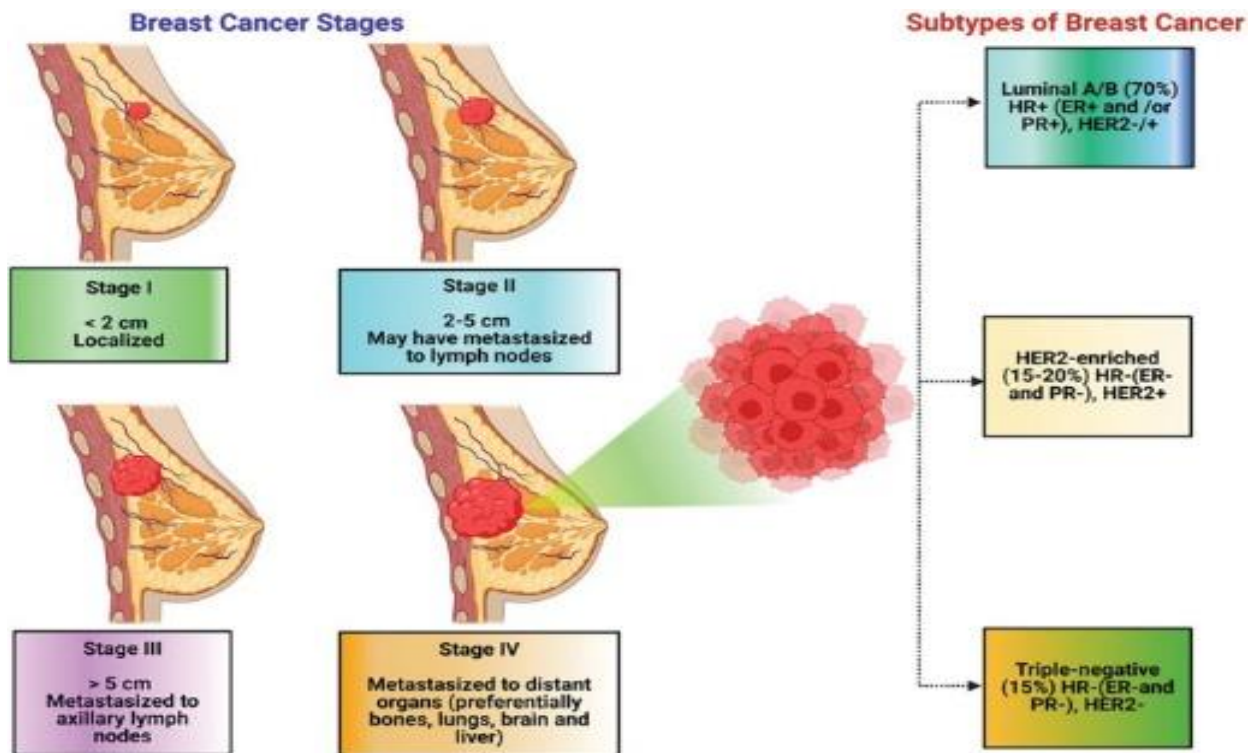
Improved cancer survival rates seen in recent decades are mainly due to advances in diagnosis and treatment, specifically reflecting advances in screening, diagnosis, and surgery (e.g., pathological staging, thoracoscopic surgery). Therapies for metastatic disease include targeted therapy (e.g., precision medicine), chemotherapy, radiotherapy, immunotherapy (e.g., programmed cell death protein-1 and programmed death ligand-1 inhibitors), and novel material-based therapies . The disruptive effects of the coronavirus disease 2019 (COVID-19) pandemic on healthcare delivery include disruptive effects with respect to the diagnosis and treatment of cancer patients due to delays in diagnosis and treatment, reduced access to care, and delays or closures of healthcare facilities and systems. These factors are likely to result in short-term, spurious declines in cancer rates followed by an increase in advanced disease and associated cancer mortality rates.

Breast Cancer

Women comprise 49.5 percent of the global population, and are disproportionately represented among elderly people over age 60. In fact, due to population growth and aging, the global cancer burden for women has been increasing in all countries regardless of income level. Breast cancer is the most common malignancy among women worldwide, with one study estimating that approximately 160,000 patients with advanced breast cancer were diagnosed in the United States as of 2017 .

There are differences in prognosis among breast cancer subtypes. Approximately 10-15% of TNBC cases present with poor prognoses due to the lack of targeted therapy for TNBC, aside from chemotherapy . Morphologically, approximately 90% of TNBC cases present as infiltrating ductal carcinoma, while the remaining cases are classified as apocrine carcinoma, lobular carcinoma, adenoid cystic carcinoma, and metaplastic carcinoma. There are six different TNBC subtypes, including basal like 1, basal like 2, mesenchymal like, mesenchymal stem like, intracavitary androgen receptor, and immune regulation subtypes. TNBC heterogeneity clinically refers to different breast cancer subtypes presenting with a triple negative phenotype. Gene expression profiles and genetic outcomes for each class show differences, thus illustrating the inherent complexity of TNBC .

TRIPLE NEGATIVE BREAST CANCER



Triple-negative breast cancer is more likely to recur as compared with other breast cancer subtypes, with five-year specific survival rates of 85% for stage 3 triple-negative cancer, as compared with survival rates ranging from 94-99% for hormone receptor-positive and ERBB2-positive cancers. The distribution of breast cancer molecular subtypes varies by race, with African and African American women having the highest rates of TNBC. TNBC presents with a higher rate of metastasis and the highest proportion of poorly differentiated or undifferentiated grades among all subtypes. These factors result in reduced survival rates .fig1

Breast Cancer Diagnosis and Treatment

Therapeutic strategies for treating breast cancer include local therapies (e.g., surgery, radiotherapy) as well as systemic therapies. Molecular subtypes have a profound influence on the therapeutic strategies selected for breast cancer. Specifically, systemic therapies have been developed primarily on the basis of molecular characteristics, including targeted chemotherapy, endocrine therapy for hormone receptor-positive diseases, anti-HER2 therapy for HER2-positive diseases, polymerase inhibitors for *BRCA* mutation carriers, and novel immunotherapy modalities.

In addition to surgical topical treatment, patients with hormone-receptor-positive cancer need endocrine therapy. A few of these patients also receive chemotherapy. Patients with ERBB2-positive cancer are treated with ERBB2-targeted antibodies or small molecule inhibitors combined with chemotherapy. Patients with triple-negative cancer typically receive only chemotherapy or radiation. Whether breast cancer patients receive radiotherapy is determined according to their specific indications. More and more patients are choosing to undergo systemic treatments, including targeted preoperative chemotherapy (i.e., neoadjuvant chemotherapy) following preoperative puncture examination. Breast cancer treatments based on nanotechnology are the focus of the current review.

Herbal medicine incorporated nanotechnology

Nanotechnology-infused herbal medicine has a significant therapeutic effect with few side effects. Nanotechnology Of NDSS is applied to cancer therapy to achieve target drug delivery, selectivity, specificity, safety, effectiveness, Frequent dose reduction, and decrease the use of conventional drugs. The increased surface area leads to quick dissolution. In BBB, permeation, and retention take place. Low toxicity ensures a sustained therapeutic effect. Enhanced absorption And solubility and decreased elimination are two effects of nanotechnology.

Nanotechnology platforms for herbal drug delivery

2.1 Types of Nanocarrier Systems

2.1.1 Liposomes and Lipid-Based Nanoparticles

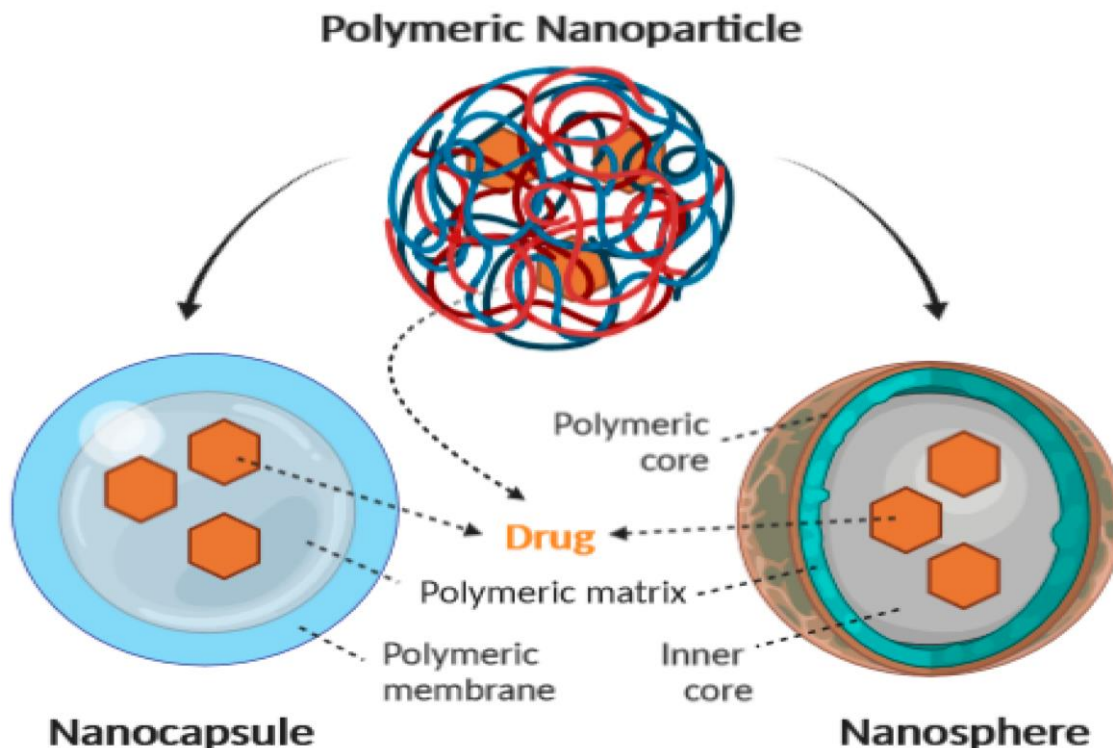
posed of lipid bilayers that can encapsulate both hydrophilic and hydrophobic posed of lipid bilayers that can encapsulate both hydrophilic and hydrophobic Liposomes are spherical vesicles composed of lipid bilayers that can encapsulate both hydrophilic and hydrophobic compounds. They offer excellent biocompatibility and biodegradability (Akbarzadeh et al., 2013). Solid lipid

compounds. They offer excellent biocompatibility and biodegradability (Akbarzadeh et al., 2013). Solid lipid compounds. They offer excellent biocompatibility and biodegradability (Akbarzadeh et al., 2013). Solid lipid advantages of controlled release and improved nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) provide advantages of controlled release and improved nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) provide stability. . TNBC cells with loaded liposomes have demonstrated enhanced cytotoxicity in MDA-MB-231 TNBC cells.

Example: Curcumin-loaded liposomes have demonstrated enhanced cytotoxicity in MDAIC50 values significantly lower than free curcumin (Li et al., 2012). IC50 values significantly lower than free curcumin (Li et al., 2012).

2.1.2 .polymeric Nanoparticles

Polymeric nanoparticles utilize biodegradable polymers such as PLGA (poly lactic-co-glycolic acid), PLA (poly lactic acid), chitosan, and alginate. These systems offer versatile drug loading, controlled release kinetics, and surface modification possibilities (Danhier et al., 2012).

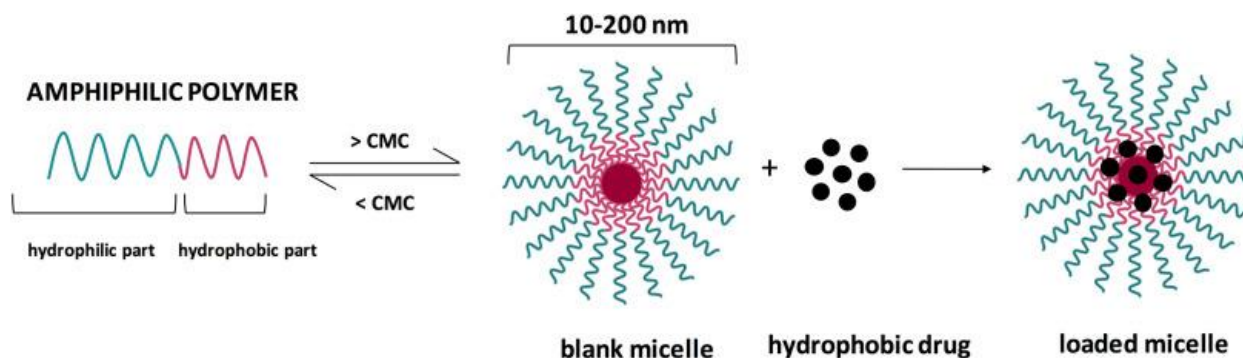


POLYMERIC NANOPARTICLES

Example: PLGA nanoparticles loaded with resveratrol showed enhanced anticancer activity against TNBC cells through improved cellular uptake and sustained drug release (Singh et al., 2014).

2.1.3 Polymeric Micelles

Polymeric micelles are self-assembled nanostructures formed by amphiphilic block copolymers with a hydrophobic core and hydrophilic shell. They are particularly suitable for encapsulating poorly water-soluble phytochemicals (Cabral et al., 2011).



POLYMERIC MICELLES

2.1.4 Dendrimers

Dendrimers are highly branched, monodisperse macromolecules with well-defined structure. PAMAM (polyamidoamine) dendrimers are commonly used for drug delivery with multiple functional groups for drug conjugation and targeting ligand attachment (Svenson & Tomalia, 2005).

2.1.5 Metallic Nanoparticles

Gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), and other metallic nanoparticles can be functionalized with biocompatibility (Dreaden et al., 2012).

2.1.6 Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) provide high surface area, tunable pore size, excellent biocompatibility, and capacity for surface functionalization (Tang et al., 2012).

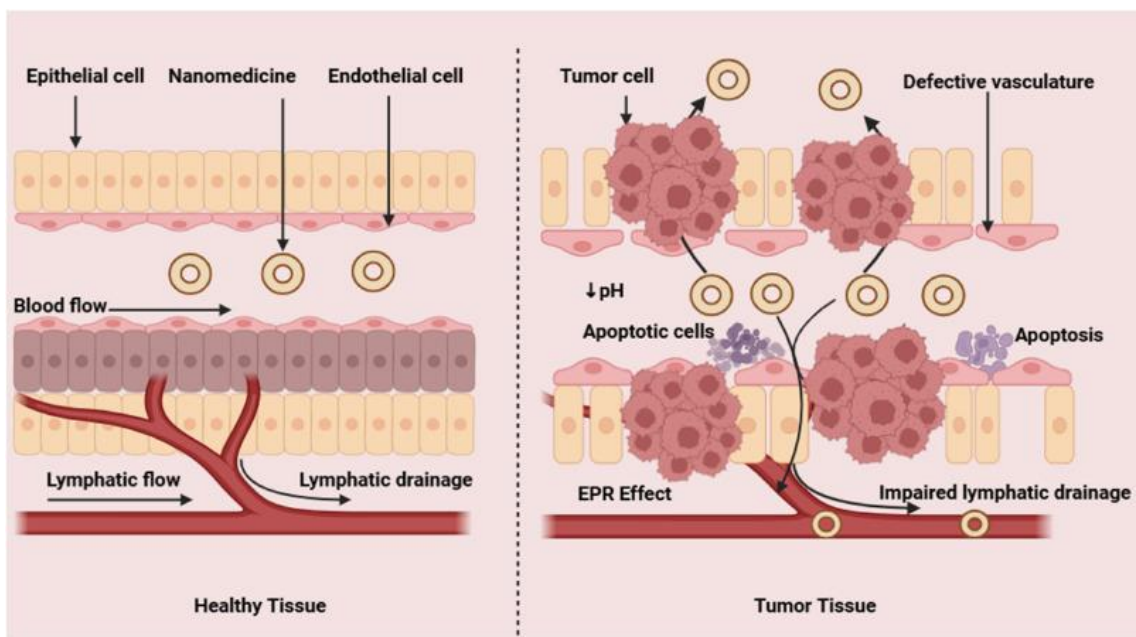
2.1.7 Nano emulsions

Oil-in-water or water-in-oil Nanoemulsions improve solubility and absorption of lipophilic phytochemicals with droplet 200 nm (McClements, 2012).

2.2 Targeting Strategies

1. Passive Targeting

The enhanced permeability and retention (EPR) effect allows nanoparticles (typically 10-200nm) accumulate in tumor tissues due to leaky tumor vasculature and impaired lymphatic drainage (Maeda et al., 2000).



PASSIVE TARGETTING

Challenges in triple negative breast cancer (TNBC)

2.1. Tumour microenvironment (TME) and immuno-suppression in TNBC

TME components can interact with each other, altering the tumor's internal environment (Fig. 1) and promoting resistance in TNBC. The TME's non-cancerous cells are essential to the development of cancer because they support the tumor's survival, growth, metastasis, and resistance to treatment. Cancer growth and medication resistance are associated with interactions between the stromal cells and the cancer cells within the TME. Oxidative stress, acidosis, and hypoxia can result from TNBC tumors' cells' proliferation, metabolic

remodeling, and cell death. These conditions can induce Lysol oxidase (LOX) activation, reshaping the ECM and promoting drug resistance.⁴⁵ Reactive oxygen species (ROS) and oxidative phosphorylation levels are decreased when the collagen prolyl4-hydroxylase P4H-a1/HIF-1 axis is activated, increasing the stemless of TNBC cells.⁴⁶ By releasing cytokines, chemokines, and ECM remodeling factors, cancer-associated .oblasts(CAFs) accelerate the spread of cancer and treatment resis-tance.⁴⁷ Lipid-associated macrophages (LAMs) generated by CAFs mediate immunological suppression in breast cancer, especially TNBC.⁴⁸ This metabolic change contributes to immunosuppression by affecting immune cell activity and causing a phenotypic change in macrophages .The activation of immunological checkpoint pathways such as the CTLA-4 (cytotoxic T lymphocyte-associated antigen-4) pathway and the PD-1/PDL1 (programmed death ligand-1) axis, among other factors, results immune suppressive responses at the tumor site.⁴⁹ ACSL3 in TNBC protects TNBC cells from Ferro ptosis induced by maternal adipocytes. M2 macrophages activate PCAT6 and release VEGF, promo.

2.2. Lack of target receptors

TNBC is the most aggressive and diverse subtype of breast cancer; it does not express the ER, PR, or HER2 markers. TNBC is identified in 15–20% of all breast cancers. TNBC, often linked to BRCA1 mutations, lacks estrogen and progesterone receptors due to mutations or epigenetic changes. Hormone therapies like tamoxifen or aromatase inhibitors can block cancer growth by interfering with hormone-driven signaling pathways. However, in TNBC, the lack of ER and PR receptors makes it difficult to control the tumor with hormonal treatments, making it more challenging to treat. TNBC does not overexpress HER2, a growth-promoting protein found on some breast cancer cells, unlike other types of breast cancer. This is due to the cancer's unique molecular characteristics, which typically show normal HER2 gene expression or lack of amplification. Targeted therapies like trastuzumab and pertuzumab are ineffective without HER2 overexpression, limiting.

2.3. Drug-resistance

MYC and MCL1 oncogenes are frequently found in therapy-resistant TNBC cells post-neoadjuvant chemotherapy. They increase mitochondrial oxidative phosphorylation (mtOXPHOS) and ROS generation, regulating drug-resistant cancer stem cells (CSCs). This stimulates HIF-1 α , which is related to CSC enrichment in TNBC. Inhibiting MYC and MCL1-targeting siRNA is one possible strategy to prevent chemotherapy resistance in TNBC by focussing on mitochondrial respiration and HIF-1 α . Twist-related protein (TWIST) increases the risk of disease recurrence and poor prognosis in TNBC patients by stimulating the EMT, promoting CSCs, and decreasing apoptosis.

The discovery that neo-adjuvant chemotherapy enhanced ABCC1 protein expression in TNBC lends greater credence to the involvement of ABCC1 in TNBC chemo-resistance. Furthermore, TNBC cells developed drug resistance as a result of the hedgehog pathway's activation because ABC transporters were upregulated. The chemo-resistance of stem cells in TNBC is significantly influenced by ABCG2.

Drug resistance is linked to the PI3K system, and intrinsic tolerance is a common side effect of inhibitors, especially PI3K inhibitors. Regarding the problem of medication resistance in TNBC patients, several advancements have been made. The primary cause of PI3K/AKT inhibitor resistance was PTEN insufficiency, which is present in 35% of TNBCs.

2.4. Drug bioavailability

The ideal loading and release profiles for Nano carrier TNBC therapy are still elusive despite effective drug loading inside Nano carriers and regulated release kinetics. Stability and bioavailability must be guaranteed by carefully designing the encapsulation procedure. Furthermore, toxicity and biocompatibility are important

variables affecting the clinical feasibility of Nano carriers. table 1 gives the summary of various NP based drugs under clinical trials for the treatment of TNBC.

2.5. Obstacles to Nano technological interventions in TNBC

Polymeric NPs, like liposomes, face biological barriers in clinical studies. For instance, CT-2103, a poly-L-glutamic acid conjugated PTX NP, administered IV produced a higher PTX AUC in the liver than in the primary tumor. Additional obstacles to tumor targeting may arise from the passive filtering of small polymeric particles through the glomerulus. Large polymeric particles may concentrate in renal cells and tissues, according to a new study, underscoring the need for comprehending drug carrier bio distribution for efficient tumor targeting. Pharmaceutical drug carriers in clinical studies often face biological barriers before reaching tumors. Combination therapy could improve efficacy or decrease toxicity, but sequential infusions limit drug synchronicity. To optimize the cytotoxic impact, the perfect carrier would target and provide a therapeutically appropriate mix of chemotherapeutic medications. illustrates the various challenges in TNBC.

Nanomaterials as Adjuvant immunotherapy for TNBC

The immune microenvironment affects the occurrence and development of breast cancer according to the principles of immune monitoring and immune editing. In the early stages of tumor genesis, the immune microenvironment plays an anti-cancer role mainly through the cytokine environment (i.e., activated CD8⁺ and CD4⁺ T cells). In contrast, once the cancer becomes aggressive, the cellular composition of the microenvironment, including fibroblasts and the cytokine content associated with cancer, facilitates cancer promotion and is invaded by breast cancer cells .

Using immune cells within targeted cancer therapy is in line with the concept of using internal mechanisms within the host immune system to fight cancer. In this study, Prof. James Allison and Prof. Tasks Honor, the winners of the 2018 Nobel Prize in Medicine, investigated the use of immune checkpoint blockades in cancer treatment *via* inhibiting negative immune regulation. Immunotherapy has achieved some success thus far, thereby providing a new therapeutic strategy for TNBC treatment. Current immunotherapies include immune checkpoint blockers, cytotoxic T lymphocyte (CTL) exchange activation, adaptive cell transfer therapy (ACT), and TME regulation. Nanotechnology presents a novel immunomodulatory strategy that can be implemented as a personalized immunotherapy modality for TNBC.

Vaccines Based on Nanotechnology

Cancer vaccines are comprised of cancer cells and/or cancer antigens and lead to an effective anti-cancer host immune response. Cancer vaccines include DNA vaccines, Ab vaccines against idiotypic types and cancer-associated pathogens, and dendritic cell vaccines . In Liu's study, the researchers (including the authors of the current review) constructed nanoparticles to deliver an mRNA vaccine encoding the cancer-associated antigen MUC1 to dendritic cells (DCs) in lymph nodes, thus activating cancer-specific T cells. In this study, combining a simple mRNA vaccine with an anti-CTLA-4 monoclonal antibody meaningfully enhanced the anti-cancer host immune response and anti-cancer effects. These data support the use NP as messenger RNA vaccine vectors as well as the combined implementation of TNBC immunotherapies, NP-based messenger RNA vaccines, and CTLA-4 inhibitors .

TREATMENT ISSUES IN TNBC

With high paces of metastasis and backslide, the forceful neoplasm physiologically displays rot in bosom cells with lymphocytic stroma. Options for chemotherapy-based TNBC treatment rely on the physiology of these

diverse cancers exhibit. DNA-damaging and anti mitotic medicines have a positive impact on BL1 tumors ,and tyrosine kinase inhibitors and drugs that target the downstream effects of the genetic change were successful against BL2tumors .SRC and PI3K inhibitors are used to treat the mesenchymal with elevated levels of EMT. Because of different cancers and the shortfall of viable oncogenetic targets along with MDR, genetic changes, and immune resistance, pathological complete response (pCR) has faced significant therapeutic challenges. Breast cancer genes BRCA1/2 and p53 (related to tumor suppression and crucial for DNA repair) abnormal expression cause taxane-and platinum-based treatments resulted in altered chemo sensitivity . The efficiency of anthracycline is impacted by surface CD73 protein overexpression. The anti-apoptotic MCL1 properties, the BRCA1/2, p53, retinoblastoma (RB1), PTEN, Janus kinase-2 (JAK2), PIK3,cyclin-subordinate CDK4/CDKN2A, and the proto-oncogene Myc affected by post-neoadjuvant chemotherapy (61) and also been connected to illness relapse and unsuccessful treatments. Biomarkers used for effective targeting. BRCA signaling linked DNA fix in ordinary cell capability and this quality was noted for the transformation (protection from DNA harming chemotherapeutic and metastasis). Drugs that hinder PARP1 are used in the reduction of tumors and the reversal of treatment resistance to taxanes and anthracyclines. Additionally, TNBC's development, invasion, dissemination, and angiogenesis have all been linked to the excessive expression of several receptors, such as VEGFR and EGFR .surface proteins targeted drugs enhance PFS with no effect on OS and pCR .LAR protein restraint enhances tumor regression with reduced metastasis .The overexpression of the transmembrane proteins programmed cell death 1 and its ligand by tumor shows confer immune resistance, the suppression of apoptosis, T-effector-to-Treg cell conversion, and enhanced cellular death of T-effector. A small statistically significant decrease in PFS has been observed with anti- , anti-PD-1, and anti-CTLA-4 drugs . The up regulation of the proteins CD44/CD24, STAT3, and ALDH1 causes treatment failure for the BL1/BL2 subtype of TNBC.

Conclusion

Triple-negative breast cancer remains a formidable clinical challenge, with limited targeted treatment options and poor prognosis. Herbal nanotechnology represents a promising and innovative approach that therapeutic potential of phytochemicals with the delivery advantages of nanotechnology platforms. This convergence addresses key limitations of both conventional chemotherapy and free herbal compound

Acknowledgement

Due to its critical dissimilarity and low related endurance rates, triple-negative bosom disease is a difficult and unmanageable condition. The most recent advancements in cancer therapy nanoparticles, particularly in British Columbia (TNBC). The special qualities of source cells (leucocyte, erythrocyte, stem cells, thrombocytes, cancer cells, antibody, etc.) utilized as a transporter for remedial conveyance utilizing NDDS. These qualities include being immune system-unaffected and having a prolonged circulation time, as well as inherent biocompatibility and biodegradability, drawn out life length, bond, and homologous focusing on. Therefore, nanoparticles coated with cellular membranes produce biomimetic nan platforms that have excellent biocompatibility and minimal immunogenicity; it is crucial to concentrate on their upcoming translation into the clinic. Nanoelectromechanical systems currently (NEMS) are employed to track exosomes unique to the tumor and not found in healthy pluripotent canter.

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