



Review article

Recent advancements in nanoconstructs for the theranostics applications for triple negative breast cancer



Ashutosh Gupta^a, Kumar Nishchaya^b, Moumita Saha^a, Gaurisha Alias Resha Ramnath Naik^b, Sarika Yadav^c, Shreya Srivastava^d, Amrita Arup Roy^b, Sudheer Moorkoth^a, Srinivas Mutalik^b, Namdev Dhas^{b,*}

^a Department of Pharmaceutical Quality Assurance, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education (MAHE), Manipal, Udupi, Karnataka State, 576104, India

^b Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education (MAHE), Manipal, Udupi, Karnataka State, 576104, India

^c CSIR-Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh, 226001, India

^d Goel Institute of Pharmacy and Sciences, Lucknow, Uttar Pradesh, 226019, India

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ABSTRACT

Cancer is a major public health concern worldwide; it is the second-highest cause of death in the United States. According to projections of cancer incidence and mortality rates throughout the world for the year 2023, triple-negative breast cancer (TNBC) is expected to be the leading cause of cancer related death among women worldwide. Traditional strategies for the treatment of TNBC have many drawbacks, such as drug resistance, toxicity etc. Discovering novel treatment delivery techniques and researching innovative, efficient drug delivery methods is important. This review discusses the types and subtypes of TNBC. The problems associated with standard therapies, mechanism of drug resistance for TNBC and highlights the need to develop novel therapeutic strategies. It provides information on the relative prevalence and severity of TNBC in the world of cancer. Several treatment approaches viz. targeted therapy, gene therapy, bacterial-mediated therapy, nanomedicine, immune checkpoint inhibitors, theranostic, radiotherapy, chemotherapy, immunotherapy, herbal therapy, and AI-based treatment for TNBC, are discussed in detail. Additionally, diagnostic techniques, including imaging and biopsy, gene expression profiling, mammography, magnetic resonance imaging, ultrasound, computed tomography scan, positron emission tomography scan, and immunohistochemistry, have been discussed in the review for effective cancer treatment. This in-depth analysis highlights the need for innovative and individualized TNBC care methods to serve patients better.

1. Introduction

Cancer has long been a significant public health crisis in the world, indicated by the complex progression of disease conditions that are evidenced by a gradual loss of growth control [1]. The challenge lies in the specific diagnosis of cancer due to the diverse tissues it affects. Among different types of cancer, breast cancer projects as the most dominant form and the primary reason for cancer-related deaths in women worldwide, contributing significantly as the second-leading cause of mortality in 2022 [2,3].

Breast cancer (BC) is a heterogenous condition with numerous genomic transformations that lead to a metastatic state. The new

incidences of invasive BC in 2023 were expected to be 279,790 in women of the USA, alongside 55,720 new incidences of DCIS. Similarly, 2800 new cases were expected to be diagnosed in men [4]. The rate of BC incidences is undergoing a gradual increase of about 0.5% per year since the mid-2000s. From birth to death, females have a 12.9% (1 in 8) chance of developing breast cancer, which varies from 2.1% to 7.0% by age. A statistical study from 2023 states that breast cancer accounts for 31% of all new diagnoses in women. The risk for a man to be diagnosed with BC is about 1 in 833, which amounts to less than 1% of all BC cases in the USA. Of the estimated 3,00,590 new breast cancer cases and 43,700 deaths for both genders in the United States, 2800 and 530 were in males respectively and 2,97,790 and 43,170 respectively were estimated

* Corresponding author.

E-mail address: namdevdhas89@gmail.com (N. Dhas).

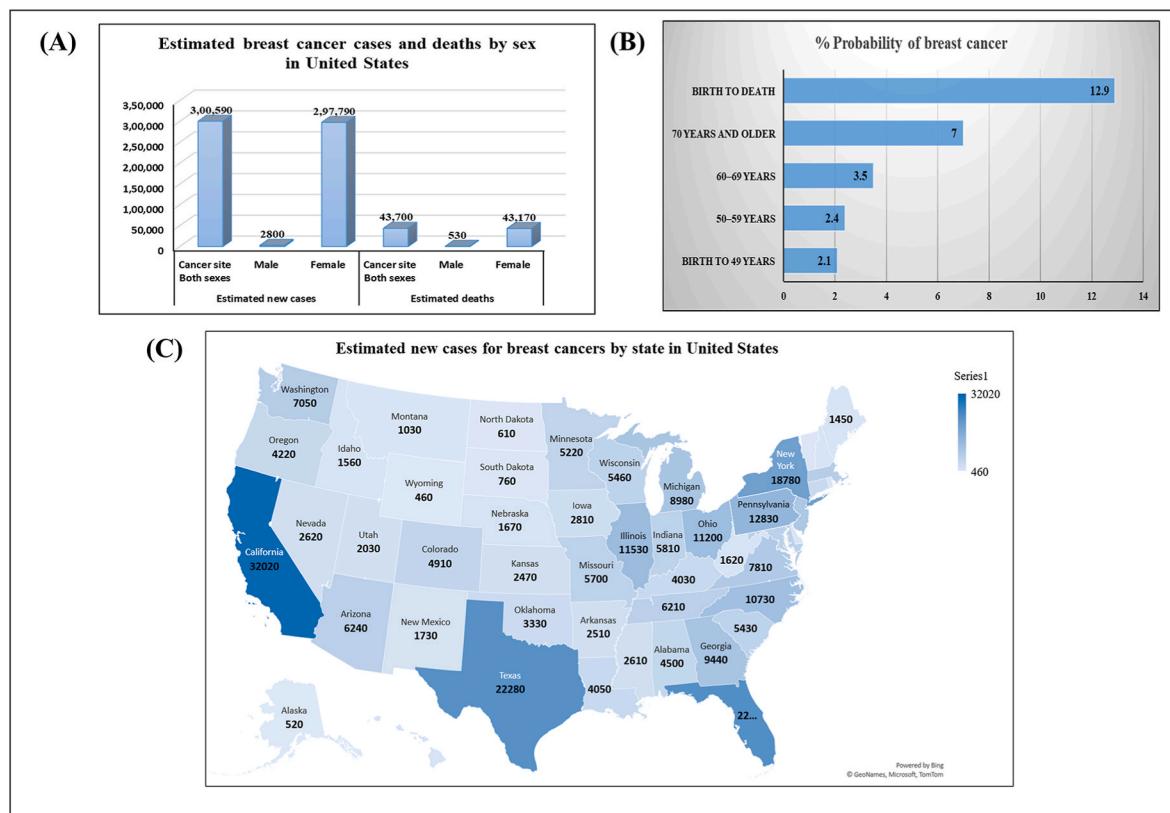


Fig. 1. Statistics of TNBC (A) Estimated breast cancer cases and deaths by sex in United States, (B) % Probability of breast cancer, (C) Estimated new cases for breast cancers by state in United States Modified from Ref (2).

in females. The highest number of estimated new cases in the USA is in California, around 32,020, whereas the lowest is in Wyoming, i.e., 460 [5].

The basic pathogenesis explains genetic expression and alteration in the patterns in three of the primary targets. These cancer subtypes differ based on their receptor profile, whether present (+) or absent (-), in the BC subtype. The lack of overexpression or amplification of the human epidermal growth factor receptor 2 (HER-2), estrogen receptors (ER) and progesterone receptors (PR) are characteristics of triple-negative breast cancer (TNBC). It counts for 10–20% of newly diagnosed occurrences of BC worldwide and that of 12% in the USA. It frequently affects young women, particularly those of African ancestry [6,7]. Especially in comparison to those European American women, African American women have an increased incidence of TNBC with deteriorated clinical manifestations [8]. Breast cancer statistics showed in Fig. 1.

TNBC includes a large spectral range of breast malignancies. It is also highly heterogeneous and is divided into many subtypes based on histology, molecule features, and clinical behavior [9]. TNBC is well known for its high recurrence and poor prognosis with a 5-year survival rate of 8–16% lower than rest of the breast cancers [10]. Women below the age of 40 are more likely to have it diagnosed. It can spread swiftly and is extremely aggressive [11]. Its resistance to hormone therapy further complicates the circumstances of the incidence [12]. The unique challenge posed by TNBC is that it is an aggressive type which spreads rapidly as cells multiply, and a lack of progesterone and oestrogen receptors implies that it is resistant to hormonal therapy making it more serious than other types of breast cancers [13]. In contrast to the other types, which spread to the bone and soft tissues, TNBC mostly affects the brain and lungs.

According to cancer statistics and studies it is seen that Asian countries has higher proportion of aggressive subtype of TNBC [14]. Specially in India, around 1,00,000 people are diagnosed with BC

annually. With global cancer incidence and deaths expected to reach 29.8 million and 16.93 million respectively, by the year 2025, the rising prevalence is attributed to factors like urbanization, aging population, unhealthy lifestyles and pollution [15–17]. In India, like the USA, breast cancer is the second leading most common cancer after lung cancer. Diagnosis of breast cancer is the major obstacle in the proper management of the disease. Around 90% in the high-income countries, 60% in India and 40% in South Africa is the survival rate according to WHO [4, 18].

The current treatment available for TNBC is chemotherapy, radiation therapy and hormone therapy in traditional delivery approach. However, these therapies often fail to eradicate the tumor because of the insufficient drug delivery to the tumor site and may cause the recurrence of the tumor. Thus, the treatment of TNBC has been a challenge for the medical practitioners. The TME and genomic characteristics play a vital role in the pathogenesis of TNBC and a thorough knowledge of these factors is essential for the development of newer strategies to combat the disease. This article aims to probe into the complexities of TNBC including its current treatment modalities, recent advancement with respect to therapeutic and diagnostic applications and the future prospects. We intend to comprehensively explore these factors and contribute to gaining an in-depth understanding of TNBC and help in devising efficient strategies for the treatment of TNBC.

1.1. Types of breast cancer

In the year 2000, Perou and Sorlie introduced a fundamental sorting system for Breast Cancer, which recognized 4 distinct subtypes: luminal A and luminal B (characterized by the presence of the estrogen receptor (ER)), basal-like, and HER2-enriched (characterized by the absence of ER expression). The reclassification of BC clinical management has shifted from a focus on tumor burden to a more biologically-centered

approach. Hormone receptor-positive breast malignancies refer to BCs that exhibit the presence of ER and progesterone receptor (PR). At the same time, TNBC is characterized by the absence of ER, PR, and HER2 expression.

Based on histological and molecular characteristics, the current clinical approach commonly utilizes an approximate categorization of five subtypes. BC subtypes include Triple negative, HER-2 enriched (non-luminal), Luminal B-like HER2+, Luminal B-like HER2-, and Luminal A-like [19].

1.2. Subtypes of TNBC

TNBC subtyping is based on biological and clinical attributes which may aid in identifying therapeutic markers, optimizing designs for a clinical trial, and stratifying patient risk [20].

1.2.1. Histological classification of triple-negative breast cancer as per WHO classification

Invasive Carcinomas: Invasive carcinomas are also known as infiltrating breast cancer and are classified into **Invasive Ductal carcinoma – No Special Type (IDC-NST)**, **Triple Negative Invasive Lobular Carcinoma (TN-ILC)**, and **Metaplastic Carcinoma**. The high-grade IDC-NST is characterized by pushing non-invasive borders, widespread geographic necrosis, an absence of nuclear pleomorphism differentiation, increased mitotic activity, and a rapid inflammatory infiltrate [21]. IDC shows poorly differentiated cells with a surrounding lymphoplasmacytic invasion and well-circumscribed having medullary features. DCIS is considered to be a precursor of IDC. The transformation of normal tissue to DCIS and IDC leads to a gradual rise in tissue stiffness, which is highest at the invasive front [22]. It is characterized by cytokeratin 5/6 positivity and a high rate of TP53 mutation.

ILC is the second most prevalent histologic BC, constituting about 5–15%. They tend to be large, multifocal, slow growing and are more than often mammographically occult [23]. Lobular carcinoma comprises loosened monomorphic cells that lack tubule formation due to the inactivation of E-cadherin, a cell adhesion molecule [24]. E-cadherin expression is reduced or absent in 84 % of invasive lobular carcinomas [25].

MpCC is a very rare type of breast cancer. It contains heterogenous group neoplasm, including the epithelial cell and mesenchymal cell. It accounts for 0.2–5% of all types of breast cancer. The Triple negative phenotype of MpBC is more therapeutically aggressive and has a poorer prognosis than that of TNBC [26]. The MpBC is categorized into 5 subtypes: spindle cell carcinoma (SpCC), squamous cell carcinoma (SqCC), matrix-producing carcinoma, and mixed carcinoma. SpCC is a highly aggressive variant of highly atypical spindle-cell, with necrosis and numerous mitotic figures [28]. Less than 0.3% of the diagnosed cancers are of SpCC [27]. Metaplastic SqCC is an aggressive carcinoma that amounts to less than 0.1% of BCs. SqCC must be suspected if atypical squamous epithelial is adjacent to atypical ductal epithelial [28]. Matrix Producing carcinoma (MPC) is a frequently diagnosed subtype of MpBC and has well demarcated nodules with central necrosis with a chondroid and osteoid matrix. Around 94% of MPC has a large area of necrosis occupying 47% of the tumor area with a peripheral ring. It has been associated with micro-glandular adenosis [28–30]. Mixed Metaplastic BC includes chondroid metaplasia, carcinosarcoma, and osseous metaplasia carcinoma [26]. It is rare; not many cases have been diagnosed in this subtype [31].

Salivary Gland type Breast tumor are rare tumors that pose a challenge in the diagnosis. They are subcategorised into **Adenoid Cystic Carcinoma (AdCC)** and **Secretory Breast Carcinoma (SBC)**. AdCC has characteristics overlying to those of the basal-like subtype of TNBC [32]. AdCC is a type of salivary gland type tumor in the breast. There are three AdCC i.e. Classic, Solid basaloid, and AdCC with high-grade transformation [33]. The tumors of AdCC were well differentiated, grade 1, with negative axillary lymph nodes. A good prognosis of TNBC

with AdCC was reported [34]. SBC is a rare and low-grade TNBC variant. SBC is a movable, palpable, well-circumscribed mass present in the subareolar region, which is tan to yellow in color and round or angulated in shape, having a vacuolated or finely granulated cytoplasm. SBCs have a good prognosis and are sometimes presented with axillary lymph node metastasis. It has three main morphological components: solid, tubular, and microcystic [35,36].

Neuroendocrine Neoplasm: Neuroendocrine carcinomas are characterized by metastatic well-differentiated endocrine-neoplasm of visceral origin. It is highly aggressive and has small-cell as well as large-cell carcinomas. Neuroendocrine differentiation is common in BC [37, 38]. They are negative for GATA3 and TRPS1 as they originate from breast cancer-specific stem cells [39].

Very rare type: As the name suggests, these carcinomas are very rare. They are classified into subtypes. It includes a subtype of **Invasive Breast Carcinoma** that is **Mucinous Cystadenocarcinoma**. It has unique features like a high-columnal cell enriched with intracellular mucin and a lumen containing high levels of extracellular mucin. Genomically these tumors are characterized by PI3CA, RB1, CRAS3, and TP53 mutations [40,41]. Also subtypes of **Salivary gland-type breast tumor** are included in rare type carcinomas like **Acinic Cell Carcinoma (AcCC)**, which is a Triple negative phenotype and is like AcCC of the salivary gland. It is less aggressive than TNBC. It shows a serous acinar differentiation along with zymogen-like granules in its cytoplasm [42, 43]. AcCC is usually benign but can occasionally cause metastasis [44]. **Mucoepidermoid Carcinoma (MEC)** is identified by basaloid, epidermoid, intermediate, and mucinous cells in a solid and cystic arrangement. MEC has characteristic MAML2 rearrangements and lacks TP53. The MEC of a breast is very similar to that of a salivary gland. It mostly affects middle-aged women [33,45,46]. **Polymorphous adenocarcinoma (PmA)** is the rarest subtype of TNBC. It is not a low-grade carcinoma, which was known for the rest Salivary gland-like carcinoma. PRKD1 mutations are the most specific feature of PmA. They are related to Tyrosine kinase receptors, PI3K pathway, NOTCH pathway, and chromatin remodelers [44–46]. **Tall-cell carcinoma with reversed polarity (TCCRP)** is a rare tall-cell variant of papillary breast carcinoma (TCVPBC), which imitates papillary thyroid cancer. The rate of lymph-node metastasis is low. The mutations observed in 90% of patients are IDH2, and 60% showed PIK3CA. They are composed of columnar epithelial cells that show reversed polarity with large cytoplasms and basally located nuclei rather than apically located [47,48].

1.2.2. Medullary carcinoma

Medullary carcinomas are rare and have specific features such as well-constrained, pushed margins and syncytial growth pattern, a moderate or marked lymphoplasmacytic invasion, and no tubule formation. MC and TNBC have a characteristic way of Genetic changes [21, 49]. Adenoid cystic carcinoma, apocrine carcinoma, and IDC-NST with medullary pattern all have a favorable prognosis, whereas the most aggressive subtypes are ILC and metaplastic carcinoma [50]. The number of positive lymph nodes increased significantly with tumor size in invasive lobular carcinoma (ILC) and mixed NST and lobular carcinoma (NST-ILC), but only slightly in metaplastic carcinoma. Despite the advent of molecular subtyping of breast cancer, the histologic classification of TNBC remains clinically significant [51].

1.2.3. Molecular classification of TNBC

1.2.3.1. Basal-like 1 (BL1). BL1 accounts for almost 35% of TNBC. BL1 is highly enriched in cell proliferation and cell cycle regulation. BL1 is of luminal progenitor origin. It has a high gene expression. It shows high Ki-67 protein expression and has a DNA damage response. DNA damage mechanisms involved in BL1 are MDM2, BRCA1, TP53, RB and PTEN [20,33,52,53]. It has a high level of basal cytokinin. It also shows a low stage, high grade, and increased overall survival without relapse [54].

PARP inhibitors, CDK inhibitors, and CHK inhibitors can target this subtype.

1.2.3.2. Basal-like 2 (BL2). BL2 is enriched in stromal and myoepithelial cells and contains epithelial cells. It originates from myoepithelial cells [55]. It expresses high growth factor levels involving signaling pathways, gluconeogenesis, and glycolysis [56]. It also has a moderate PCR rate and is susceptible to platinum and PARP inhibitors concerning BL1. It also shows an increased myoepithelial marker expression. Growth factors involved in EGF, NGF, Wnt/Catenin Signaling pathway, HGF, impaired glucose metabolism, and IGF1R. It can be targeted by therapeutic agents affecting metabolic pathways, RTK inhibitors, and by interfering with EMT [53].

1.2.3.3. Immunomodulatory (IM). IM subtype features immune cell processes and signaling cascades. It has a high immune response and a low M2-like macrophage. It has an increased expression of genes related to immune cell processes. The gene clusters include cytokine signaling, immune cell signaling, immune signal transduction pathway, and antigen presentation [57]. It has a tumor-infiltrating lymphocyte (TIL) origin. The presence of TIL is promising for prognostic markers and immune-checkpoint targeting as well as JAK/STAT pathway [58,59].

1.2.3.4. Mesenchymal (M). M subtypes are genes concerned with cell motility and EMT, show cellular proliferation gene expression, and are enriched in genes related to mesenchymal stem cells. High PAM pathway aberrations and a low PCR rate characterize it. It showed lower stromal and immune cell estimates, indicating a lack of immune cells in these tumors. Both lymphocyte and monocyte signatures were absent in the M-subtype [55]. It is also called metaplastic breast cancer, which involves highly activated signaling pathways related to cell migration, differentiation, and extra-cellular matrix interaction pathways. It is promising targeting therapies like TGF inhibitors, NOTCH, AKT, and mTOR inhibitors [58–60].

1.2.3.5. Mesenchymal stem-like (MSL). MSL subtypes are quite like the M subtype as they are enriched for cell motility and EMT genes. The MSL subtype also shows a reduced expression of cellular proliferator genes and is enriched in the mesenchymal stem cells gene. Angiogenesis genes and stemness characterize it. The potential therapies for this subtype are Src antagonists, antiangiogenic drugs, and PI3K inhibitors [11,58–60].

1.2.3.6. Luminal androgen receptor (LAR). LAR has a significantly different gene expression profile different from the rest of the TNBC subtypes. LAR subtype has a gene expression pattern like luminal types, despite being ER-negative. It is also involved in Hormone signaling and luminal gene up-regulation. The signaling pathways involved are steroid synthesis, androgen or estrogen metabolism, and porphyrin metabolism [20,60,61]. LAR is related to hormone-responsive L2-type genes [55].

Lehmann's team analyzed the genetic sequences of TNBC patients using mRNA expression profiling clustering and discovered that TNBC can be classified into six groups with different gene expression profiles and involvement in various signal transduction pathways. TNBC is made up of roughly half of BL1 and BL2 [11]. TNBC subtypes have different benign appearances, clinical features, and delay in diagnosis, which can lead to an upgrade of the tumor stage [62].

1.2.4. Molecular subtypes of TNBC based on FUSCC classification

TNBCs were classified into four mRNA subtypes with distinct molecular characteristics:

Basal-like Immuno-Suppressed (BLIS) accounts for approximately 39% of diagnosed cases of TNBC. BLIS shows downregulation of signaling pathways related to B cell, T cell, and NF-κB and cytokine networks, showing the worst prognosis. It shows an upregulation in the mitotic cell cycle, mitotic prometaphase, DNA replication, and DNA

repair [60,63]. **Basal-like Immuno-Activated/Immunomodulatory** comprises around 14% of the diagnosed cases of TNBC. It shows upregulation of the B cell, T cell, and NF-κB and cytokine networks related to genetic factors and high expression of STAT pathways, leading to excellent prognosis [60,63]. **Mesenchymal-like (MES)** constitutes about 20% of the TNBC case. It expresses an upregulation of ECM-receptor interaction, Focal adhesion, ABC transporters, TGF-β, and Adipocytokine signaling pathway [52,60,63]. **Luminal Androgen Receptor** accounts for 28% of TNBC cases. It shows an upregulation in Steroid hormone biosynthesis, porphyrin, chlorophyll, androgen and estrogen metabolism, and the PPAR signaling pathway [20,60,63].

Exploring the genomic deviations that drive each TNBC mRNA subtype added to our understanding of TNBC heterogeneity and potential therapeutic options. The development of genomics has fuelled efforts toward "precision oncology," which targets cancers based on genetic mutations [62,64].

1.2.5. DNA methylation

DNA methylation is an epigenetic marker in human cancer. Especially in TNBC, there is a lack of effective targeted therapy due to its heterogeneity. DNA methylation plays a significant role. DNA methylation plays an essential role in numerous cellular processes. DNA methylation markers are also biologically and chemically stable. Two types of methods occur in tumorigenesis: gene-specific hypermethylation and genome-wide hypomethylation. DNA methylation patterns of numerous TNBC-related genes have been found [65,66]. Few aberrations of DNA methylation have been found in TNBC, and though they do not have any diagnostic function, they have promising value in prognosis and drug response [67]. Hyper-methylation is observed at tumor-suppressor genes (TSG), whereas Hypomethylation leads to genome instability [68]. Hypermethylation is related to the inactivation of TSG, which aids in the proliferation of tumor cells [66]. Hypomethylation induces the activation of the CT83 gene, which has a high significance in TNBC [69].

2. Biology of triple negative breast cancer resistance

Prognostic factors are crucial in determining the potential outcome of a disease or condition. In this context, unfavorable prognostic factors refer to indicators linked with a lesser diagnosis and prognosis. The study population consisted of women of varying ages diagnosed with a particular condition. The data collected from medical records and patient interviews were analyzed to identify unfavorable prognostic factors. These factors included but were not limited to tumor characteristics. Upon initial diagnosis, it was observed that the lesions tend to exhibit larger sizes, less maturity, and a decreased frequency of estrogen receptors (ER) and progesterone receptors (PR). Conversely, these cases have a higher prevalence of HER2 overexpression and vascular invasion.

Ductal BC is a type of malignancy considered by the uncontrolled proliferation of luminal epithelial cells within the breast ducts. This aberrant cell growth can initially manifest as carcinoma-in-situ, a non-invasive form of cancer confined to the ductal system. However, if left untreated, carcinoma-in-situ has the potential to progress into invasive and metastatic BC, which poses a more significant threat to the patient's health and survival. The evolution from in situ cancer to invasive cancer is characterized by the disruption of the myoepithelial cell layer and the subsequent infiltration of malignant luminal epithelial cells into the surrounding stroma, ultimately leading to the development of invasive carcinoma [70].

In the context of classic invasive lobular BC (ILC), the growth pattern is distinguished by the infiltration of individual cells through the stroma while causing minimal disruption to the typical architecture of the surrounding tissue. The present study examines the spatial organization of invading tumor cells, which often exhibit a distinctive concentric (targetoid) arrangement surrounding normal ducts or structures.

Hormonal factors primarily regulate the phenomenon known as invasive lobular carcinoma (ILC). It is typically observed in individuals of advanced age and often manifests as multiple tumor sites. Furthermore, ILC tumors commonly exhibit positive expression of ER/PR while showing a negative status for the HER2-neu receptor [71].

Despite the rapid advancements in research, the precise pathophysiology of TNBC remains elusive. The current body of research encompasses various aspects related to the overexpression of the BRCA1 gene, TP53 mutation, RB1 loss, and other relevant factors. In this article, we will delve into the latest developments in understanding the pathogenesis of TNBC [19].

2.1. TP53 mutation

Several processes within the cell are controlled by the TP53 gene, also known as tumor protein 53. In addition, these processes include the cell cycle, cell proliferation, DNA repair, cellular senescence, and apoptosis. It is well-documented that cells harboring mutated TP53 can evade apoptosis and transform into aggressive tumor cells. A tumor suppressor gene such as TP53 regulates cell cycle arrest, DNA repair, and programmed cell death. It is possible for mutations to disrupt the normal function of TP53, leading to the accumulation of genetic alterations and the development of TP53-mutated tumors, which are highly invasive, poorly differentiated, and of high histologic grade, which decreases the effectiveness of therapeutic interventions. The prevalence of TP53 mutations in primary BCs ranges from 18% to 25%, with a significantly higher occurrence observed in TNBC, reaching approximately 80%. This notable disparity in TP53 mutation rates distinguishes TNBCs from other subtypes of BC. The prevailing proportion of TP53 mutations encompasses missense mutations, which give rise to mutant p53 proteins. Moreover, the heightened resistance to degradation exhibited by the mutant protein in malignant cells, as compared to the wild-type p53, renders the TP53 mutation a captivating focus for therapeutic intervention in TNBC [72,73].

2.2. BRCA1 mutations

The incidence of BRCA mutations varied from 9.3% to 15.4% across TNBC groups and 2.7%–4.2% among individuals with metastatic BC [74,75]. BRCA proteins play a crucial part in the DNA damage response, which supports the survival of both standard and cancerous breast cells [76]. Therefore, individuals who carry the BRCA gene mutation and have triple-negative TNBC are expected to exhibit sensitivity to DNA damage therapy. However, the clinical outcomes do not align with these expectations, as only a modest proportion of patients (20–40%) experience benefits from PARP inhibitors and survive for five years following diagnosis. The lack of effective therapy results in a significant proportion of patients with TNBC experiencing early recurrence and the development of distant metastases. Epigenetic silencing through promoter hypermethylation is a prominent mechanism that can lead to BRCA1 deficiency, which is considered the primary cause of malignancy associated with BRCA1 deficiency [77].

2.3. RB1 alterations

The loss of the tumor suppressor RB1 is common in various human cancers due to mutations, deletions, transcriptional silence, and hyperphosphorylation affecting its gene product, pRb. Indeed, it has been observed that approximately 20–25% of breast cancer cell lines exhibit deletions or rearrangements. The activity level of TNBC is predominantly low. Furthermore, recent progresses in the field of genomic sequencing, transcriptome analysis, epigenetic research, and proteomic inquiries have unveiled the occurrence of RB1 deletion in approximately 0.20% of TNBC. The ablation of murine Rb within the mammary epithelium results in the emergence of basal-like and luminal malignancies.

Nevertheless, the lack of both Rb and p53 results in tumors that resemble claudin-low tumors. This finding provides evidence for the involvement of RB1 in the development and progression of TNBC. A considerable proportion of patients diagnosed with luminal-B (61.5%) and Basal-like (72%) breast cancer subtypes exhibited diminished expression of the RB1 gene and experienced loss of heterozygosity (LOH) at the RB1 locus [78,79].

2.4. JAK STAT pathway

Janus kinases (JAK) are members of the non-receptor tyrosine kinase family and play a crucial role in activating STAT proteins in BC. To shut down the JAK-STAT pathway, it is essential to use several techniques that target specific JAKs. Some natural and manmade STAT inhibitors enhanced BC decrease. It was discovered that curcumin-BTP hybrids are efficient against STAT3The administration of curcumin-BTP hybrids resulted in a reduction in STAT3 phosphorylation, nuclear translocation, and the expression of genes regulated by STAT3. BMA097 was found to interact directly with the SH2 (Src Homology 2) domain of STAT3, thereby impeding the phosphorylation and activation of STAT3. Consequently, this interaction led to the suppression of genes regulated by STAT3 [80]. Han et al. also examined paclitaxel resistance in TNBC patients whose JAK2 pathway was modulated. PDX models of BC were treated with paclitaxel for four weeks however no substantial changes were observed in the transcriptomic environment. The differentially expressed genes (DEGs) linked to the response to paclitaxel predominantly pertain to developing resistance to paclitaxel rather than the acquired resistance that occurs during therapy *in vivo* [81]. Wang and his colleagues demonstrated that the JAK/STAT pathway caused Paclitaxel resistance. IL-22 used this mechanism to generate resistance in TNBC. The Wound Healing Assay was used to assess IL-22 in TNBC. Further Transwell Assays determined the increase in dosage of IL-22-treated cells [82].

2.5. MAPK-ERK pathway

Zhao et al. established that the MAPK/ERK pathway plays a role in cell viability. Significantly, increased ERK1/2 activity (phosphorylation) has been seen in metastasis locations compared to primary BCs and is more prevalent in TNBC. The chemosensitivity is regulated by the activation of ERK1/2 through FLNA. The Western Blot analysis conducted on MDA-MB-231 cells demonstrated that the downregulation of FLNA reduced FLNA protein abundance. A simultaneous decline in the phosphorylation of ERK1/2 accompanied this decrease in FLNA levels. Conversely, the restoration of FLNA expression led to the activation of ERK signaling [83]. According to scientific research, the TRPC3/RA-SA4/MAPK Pathway is crucial in regulating the proliferation and apoptosis resistance of TNBC cells [84]. Linc-RoR similarly enhances MAPK/ERK signaling and imparts estrogen-independent BC development [85].

2.6. PI3K/ATK/mTOR pathway

The progression of cancer and the development of drug resistance can be attributed to the heightened sensitivity of the PI3K/ATK/mTOR pathway. Numerous pharmaceutical agents are being developed to specifically target the PI3K/ATK/mTOR Pathway to impede the advancement of cancer stem cells. The pathways above are commonly activated in various types of carcinomas.

The PIK3CA gene is frequently mutated in breast cancer (BC), resulting in the activation of PI3K and exerting a significant influence on the development of resistance to conventional anticancer drugs. Conversely, the activation of the PI3K/AKT pathway possesses the capacity to induce the upregulation of multidrug resistance-associated protein-1 (MRP1), ABCG2, and P-glycoprotein (P-gp, also known as ABCB1), thus potentially contributing to the emergence of multidrug

resistance. Individuals who have been diagnosed with cancer and demonstrate dysregulation of the PI3K/AKT pathway are more susceptible to developing resistance to a range of treatment approaches, such as chemotherapy, endocrine therapy, HER2-targeted therapy, PARP inhibitors, and immunotherapy. The inhibition of this biological pathway holds promise in increasing drug susceptibility and mitigating the emergence of resistance. Based on the existing evidence, it can be inferred that the utilization of PI3K/AKT inhibitors in combination with other anticancer medications presents a potential approach for mitigating medication resistance in breast cancer [86,87]. Also, the PI3K/AKT/mTOR Pathway caused trastuzumab, Cisplatin, and lapatinib resistance in breast cancer [88–90].

2.7. Notch signaling

The Notch signaling pathway has been associated with various disease pathologies, including cancer. Chemotherapy administered for breast cancer has been found to elicit the activation of Notch signaling, a pathway that is observed to be upregulated in tumors that exhibit resistance to therapy. The activation of Notch signaling alone is adequate to induce resistance to chemotherapy, whereas the inhibition of Notch signaling restores the sensitivity of resistant cells to conventional treatment [91]. Using Notch inhibitors with standard chemotherapies increases *in vitro* and *in vivo* treatment effectiveness via an additive effect. In addition, Notch signaling has been primarily ascribed to the failure of inhibitors of critical pro-oncogenic signaling pathways in clinical studies [92]. For example, an examination of resistance to TNBC PI3K/mTOR inhibitors demonstrated that administering PI3K/mTOR or TORC1/2 resulted in the enrichment of breast cancer stem cells (BCSCs) accompanied by elevated expression of Notch1. The enrichment of BCSCs was impeded due to the blockage of the GSI Notch signaling pathway. Furthermore, Diluvio et al. (2018) discovered that GSI therapy had the effect of increasing the sensitivity of TNBC cells that were resistant to EGFR tyrosine kinase inhibitor (TKI), specifically gefitinib [93]. The resistance to trastuzumab and lapatinib in HER2+ breast cancer has been associated with Notch signaling. Following treatment with trastuzumab or lapatinib, there is an observed elevation in Notch signaling, accompanied by a reduction in Notch transcriptional activity in HER2-positive cells relative to HER2-negative cells [94,95].

2.8. Wnt/β-catenin signaling pathway

Wan et al. observed an upregulation of ST8SIA1 mRNA and protein expression in multiple TNBC cell lines following prolonged exposure to chemotherapeutic agents. Consistently previous studies have demonstrated that a significant proportion of patients with TNBC who developed resistance to chemotherapy exhibited elevated expression levels of the ST8SIA1 gene. The findings from mechanistic investigations have shown that the suppression of ST8SIA1 inhibits the FAK/Akt/mTOR and Wnt/β-catenin signaling pathways [96]. Similarly, Zheng et al. demonstrated that NLRP3 antagonist suppressed the EMT, IL-1, and Wnt/β-catenin signaling pathways *in vitro* in TNBC resistant to gemcitabine [97].

2.9. TGF-β signaling

The cytokine known as transforming growth factor (TGF-β) possesses multiple functions. According to recent studies, there is evidence to suggest that TGF-β influences the population of cancer stem cells, thereby potentially affecting the development of resistance to cancer medications. Xu conducted an experimental study wherein MDA-MB-231 (MB-231) cells were exposed to epirubicin. The findings demonstrated a correlation between dosage and an elevation in the concentrations of TGF-β and markers associated with breast cancer stem cells. CD44 + CD24 [98]. Chen and his colleagues demonstrated that curcumin is used to inverse the effect of doxorubicin resistance. It was seen

that TGF-β induces EMT and contributes to the metastatic development of many cancer cells. The investigation focused on examining the effect of doxorubicin on the expression of Ser465/467 phosphorylation of Smad2, as TGF-β has been shown to induce this phosphorylation. The application of Doxorubicin led to an elevation in the phosphorylation of Ser465/467 on Smad2 in BT-20 cells. SB431542, a selective inhibitor of TGF-β receptor kinase, was utilized to provide evidence that the induction of the TGF-β pathway in BT-20 cells was facilitated by doxorubicin [99].

3. Modalities for the treatment of TNBC

Despite ongoing efforts to discover new therapies, treating patients with TNBC poses significant challenges. TNBC patients do not derive benefits from hormonal therapies or trastuzumab-based treatments due to the loss of crucial receptor targets, such as estrogen receptors (ER), progesterone receptors (PGR), and human epidermal growth factor receptor 2 (HER-2) [100]. Consequently, immunotherapy surgical intervention and chemotherapy, either as standalone approaches or combined, remain the primary modalities for managing TNBC [101]. These interventions aim to remove the tumor through surgery and subsequently administer chemotherapy to eliminate any remaining cancer cells. However, it is essential to note that this approach may not fully address the diverse characteristics of TNBC, limiting the overall effectiveness of treatment.

3.1. Problem related with the available treatment of triple negative breast cancer

Breast cancer is a prevalent form of cancer among women, constituting approximately 25% of all cancer cases [102]. Within breast cancer, TNBC accounts for around 15–20% of all breast cancers. Currently, the main treatment approaches for breast cancer involve conventional chemotherapy and radiation [103]. Unfortunately, no targeted therapies approved by the FDA specifically for TNBC exist. TNBC is characterized by its aggressive nature, with a poor prognosis and a tendency for rapid proliferation and metastasis (spread to other parts of the body). Due to these challenging characteristics and the absence of approved targeted treatments, extensive efforts have been undertaken to identify potential molecular targets for TNBC [104]. However, with technological advancements, molecular subtyping of TNBC and the development of targeted therapies have progressed extensively.

Meanwhile, numerous cohort studies, clinical trials, and in-depth analyses have revealed diverse molecular alterations in TNBC, causing controversy in diagnosis and treatment. The subtyping helps understand the underlying biology and develop personalized treatment strategies [105]. With a focus on promising therapeutic approaches and problems associated with treatment options for TNBC, this section discusses critical findings and therapeutic trends in TNBC.

3.1.1. Immunotherapy challenges with TNBC

Pembrolizumab and atezolizumab, two immunotherapy drugs with promising potential in treating various cancers, including TNBC, face several challenges when explicitly used for TNBC patients [106]. The immunosuppressive tumor microenvironment prevalent in TNBC poses a significant hurdle for immunotherapy [107]. TNBC tumor cells often exhibit low expression of programmed death-ligand 1 (PD-L1), which is the target for Pembrolizumab and atezolizumab [108]. This low PD-L1 expression reduces the likelihood of a robust response to pembrolizumab and atezolizumab, which work by blocking the PD-1/PD-L1 pathway to enhance the immune response against cancer cells [109]. Moreover, the heterogeneity of TNBC further complicates the outcome of immunotherapy. TNBC patients display diverse molecular characteristics and immune profiles, resulting in varying responses to immunotherapy [110]. The identification of predictive biomarkers that can

accurately determine which TNBC patients benefit from pembrolizumab and atezolizumab remains a significant challenge. While PD-L1 expression has been proposed as a potential biomarker, its correlation with immunotherapy response in TNBC is not yet fully established [111]. TNBC cells can employ various mechanisms to evade immune recognition and attack, such as upregulating alternative immune checkpoint pathways or activating other immunosuppressive mechanisms [112]. Overcoming these resistance mechanisms is a critical challenge in achieving long-term success with immunotherapy for TNBC. To improve treatment outcomes, researchers are exploring the combination of immunotherapy with other modalities, such as chemotherapy or targeted therapies. However, determining the optimal combination regimens, dosages, and treatment sequences is an area of ongoing research. Striking the right balance between maximizing efficacy and minimizing toxicities is crucial but challenging in TNBC. With continued research and advancements, it is hoped that immunotherapy can become a more effective and personalized treatment option for TNBC patients in the future.

3.1.2. TNBC treatment challenges associated with receptor tyrosine kinases

Receptor tyrosine kinases (RTKs) are a class of transmembrane receptors with enzymatic activity that are situated on the cellular membrane. The components of these entities encompass an extracellular region responsible for ligand binding, a transmembrane helix, a protein tyrosine kinase domain, and juxtamembrane regulatory regions [113]. The family in question consists of a total of 58 distinct receptors, which encompass notable examples such as the epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), insulin-like growth factor receptor (IGFR), fibroblast growth factor receptor (FGFR), and AXL [114]. Receptor tyrosine kinases (RTKs) operate through the ligand binding process, which triggers the formation of receptor dimers and subsequent activation of signaling pathways downstream. The pathways under consideration encompass the PI3K/AKT/mTOR pathway, the RTK/Ras/MAPK pathway, and the Janus kinase/signal transducer and activator of the transcription protein family pathway [115]. The occurrence of mutations or dysregulation in receptor tyrosine kinases (RTKs) has contributed to the advancement of cancer, rendering them appealing targets for therapeutic interventions in cancer treatment [116]. As a result, there has been a growing approval by the U.S. Food and Drug Administration (FDA) for a more significant number of tyrosine kinase inhibitors (TKIs) and anti-TKI antibodies to be utilized in the treatment of cancer [17]. Targeting RTKs and associated pathways holds promise as a therapeutic approach for TNBC.

However, several challenges are associated with this strategy. It is evident that TNBC is a highly heterogeneous disease, both intratumorally and between patients. The expression and activation status of RTKs can vary significantly among TNBC patients [117]. Identifying the specific RTKs that are aberrantly activated in individual tumors is challenging. This heterogeneity necessitates a personalized approach to target the relevant RTKs for each patient.

Moreover, RTKs are often interconnected with multiple signaling pathways, making it difficult to selectively target a single RTK without affecting other pathways. These overlapping pathways can lead to compensatory mechanisms and resistance to therapy. Furthermore, TNBC cells are shown to develop resistance to RTK-targeted therapies through various mechanisms, such as mutations in the targeted RTK or downstream signaling molecules, activation of alternative pathways, or alterations in the tumor microenvironment [116]. In addition, targeted therapies directed against RTKs can have off-target effects and cause toxicity also. It is essential to carefully evaluate the potential side effects of inhibiting specific RTKs and develop strategies to mitigate these adverse events. Balancing the efficacy and tolerability of targeted therapies is a significant challenge in the clinical management of TNBC.

3.1.3. TNBC surgical challenges

In many studies, it has been determined that patients with TNBC disease are more likely to undergo mastectomy than lumpectomy [118]. Despite the association between TNBC status and younger age and higher-grade tumors, surgical treatment choice was not affected [103]. However, due to the aggressive nature of TNBC, achieving clear margins can be challenging, potentially leading to an increased risk of local recurrence and the need for additional treatments. Suppose TNBC has already spread to distant sites. In that case, surgery alone may not be curative, and a multidisciplinary approach combining surgery with systemic therapies, such as chemotherapy or targeted agents, is often required [119]. However, despite these challenges, surgery remains an integral part of the management of TNBC. Surgery plays a crucial role in removing the primary tumor, assessing lymph node involvement, and obtaining tumor tissue for further characterization and prognostic information. To optimize surgical outcomes, a multidisciplinary approach involving surgeons, medical oncologists, and radiation oncologists is essential to ensure comprehensive and personalized treatment strategies for TNBC patients [120].

3.1.4. DNA damage response (DDR) pathway challenges in TNBC treatment

The DNA damage response (DDR) pathway is crucial for maintaining genomic integrity and repairing DNA damage. TNBC often exhibits defects in the DDR machinery, including mutations in BRCA1 and BRCA2 genes [121]. These mutations impair the ability of tumor cells to repair DNA damage, leading to genomic instability and increased sensitivity to further DNA damage. Exploiting the impaired DDR pathway in TNBC cells has shown clinical benefit through poly (ADP-ribose) polymerase (PARP) inhibitors. PARP inhibitors selectively target cancer cells with DDR deficiencies, as they rely heavily on PARP-mediated DNA repair mechanisms [122]. Clinical trials have demonstrated improved outcomes in TNBC patients with BRCA mutations treated with PARP inhibitors, such as Olaparib and talizumab [123]. However, several challenges are associated with DDR pathway targeting in TNBC. For example, BRCA1 and BRCA2 mutations are reliable biomarkers for response to PARP inhibitors, but not all TNBC patients with DDR deficiencies have these mutations. Therefore, identifying additional biomarkers beyond BRCA mutations that accurately predict response to PARP inhibitors is essential [124]. There is also a possibility of acquired resistance to PARP inhibitors developing over time, which could limit their long-term efficacy [125]. Moreover, resistance mechanisms can include restoration of homologous recombination (HR) DNA repair pathways, secondary mutations in DDR genes, or activation of alternative DNA repair mechanisms [126]. Therefore, elucidating these resistance mechanisms and developing strategies to overcome them is crucial for improving the durability of response to DDR-targeted therapies. Although PARP inhibitors have demonstrated clinical advantages in TNBC patients with DNA damage response (DDR) deficiencies, their effectiveness as standalone treatments is restricted.

In contrast, the Canadian study conducted a randomized, double-blind, multicenter trial to assess the efficacy of Olaparib in conjunction with paclitaxel as an initial or subsequent therapy for metastatic TNBC and observed significant toxicity patterns [127]. Exploring combination strategies that enhance the DDR deficiency and exploit synthetic lethal interactions may improve treatment outcomes. These combinations could include other targeted agents, chemotherapy, or immunotherapies, with the goal of increasing tumor sensitivity and preventing the emergence of resistance. Additionally, optimizing clinical trial designs to efficiently evaluate the efficacy of DDR-targeted therapies, including appropriate endpoints and patient stratification strategies, is essential for translating preclinical findings into clinical practice.

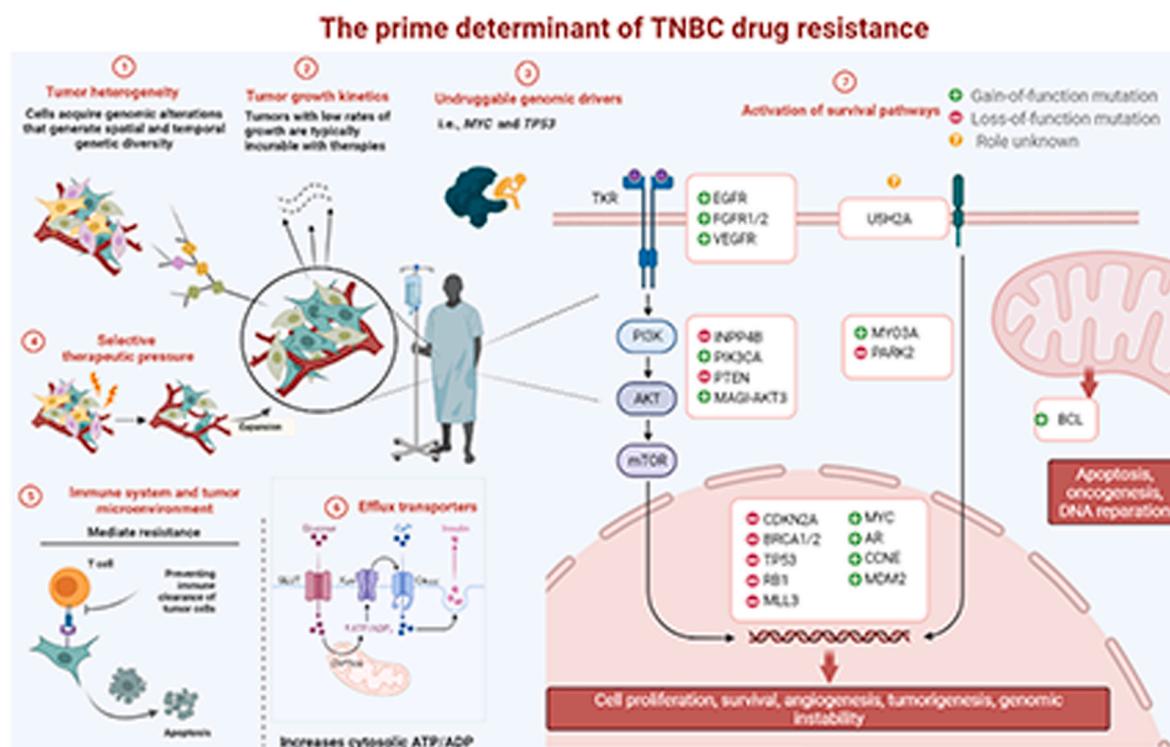


Fig. 2. The major factors for TNBC drug resistance. 1) tumor heterogeneity; 2) growth kinetics; 3) undruggable genomic drivers; 4) selective therapeutic pressure; 5) immune component; 6) Efflux transporters and 7) Activation of different survival signaling pathways.

3.2. The prime determinant for drug resistance

Drug resistance in TNBC can be regarded as a complex phenomenon that is influenced by several factors. An understanding of these determinants is crucial for developing effective treatment strategies. Here are some of the determinants that need to be considered in detail. TNBC is characterized by high genetic and phenotypic heterogeneity (Fig. 2). As a result, different subpopulations of cancer cells can have different characteristics and genetic changes within a tumor. Some subpopulations may inherently resist specific treatments, while others can adapt and develop resistance over time [128]. Tumor heterogeneity poses a challenge in effectively targeting all cancer cell populations within the tumor. TNBC tumors exhibit extensive genetic diversity, with the presence of multiple subclones or people of cells harboring different genetic alterations [129]. These genetic differences can lead to variations in tumor response to treatment. Some subclones may possess intrinsic resistance to certain drugs, while others may acquire resistance by accumulating additional mutations over time [128]. In addition, TNBC cells can exhibit phenotypic plasticity, meaning they can switch between different cell states with distinct characteristics. This plasticity allows tumor cells to adapt to changing environments and evade the effects of drugs. For example, some TNBC cells can undergo an epithelial-to-mesenchymal transition (EMT), which confers resistance to chemotherapy and promotes metastasis. Also, TNBC tumors can display intratumoral heterogeneity, in which different subregions within the same tumor display other genetic and phenotypic characteristics [130].

This heterogeneity can lead to spatial variation in treatment response, as different regions may have varying sensitivities or resistances to specific drugs. Consequently, targeting a single molecular alteration or pathway may not eradicate the tumor. Overall, the complex interplay of genetic and phenotypic heterogeneity, phenotypic plasticity, the tumor microenvironment, evolutionary adaptation, and intratumoral heterogeneity in TNBC contributes to the development of drug resistance [131]. Moreover, TNBC cells can upregulate efflux pumps, such as P-glycoprotein, which are responsible for actively pumping

chemotherapy drugs out of the cells through the efflux pumps [132]. This efflux mechanism reduces the intracellular concentration of drugs, limiting their effectiveness [133]. Multidrug resistance is associated with increased expression of drug efflux pumps within cancer cells, making it difficult for chemotherapy drugs to accumulate within them, which makes chemotherapy more effective [134]. However, the immune microenvironment can also contribute to resistance by promoting immunosuppressive factors or immune evasion mechanisms.

Interestingly, it is evident that dysregulation of specific signaling pathways can confer resistance to targeted therapies. For instance, the PI3K/AKT/mTOR pathway and the JAK/STAT pathway are frequently dysregulated in TNBC [135]. Of note, other factors within the tumor microenvironment, such as hypoxia (low oxygen levels) and acidity, can impact drug penetration and effectiveness. Hypoxic regions within tumors have reduced drug delivery due to limited blood supply, making them resistant to therapy [136]. Additionally, the acidic pH in the tumor microenvironment can influence the activity of drugs and impair their efficacy [137]. Considering all these facts, we must understand these drug resistance determinants in TNBC to develop personalized treatment approaches that target multiple pathways and overcome resistance mechanisms.

4. Novel approaches for combating the drug resistance

TNBC is a subtype of conventional breast cancer that lacks some specific expressions such PR, ER and HER2 [138,139]. Furthermore, novel approaches for TNBCs were not so much successful in the early 20s. The unavailability of diagnostics advancement, lack of certain receptors collectively worsen the treatment to breast cancer. The pathogenesis of TNBCs explains the deficiencies of progesterone and estrogen receptors with gene amplification related to HER2 gene. The tumor microenvironment and several heterogeneous factors contribute to the growth of TNBCs [140,141]. Besides, the chemoresistance of anti-cancer agents is a major hurdle for effective treatment. Numerous mechanisms support chemoresistance, especially transporter-regulated drug efflux accounts

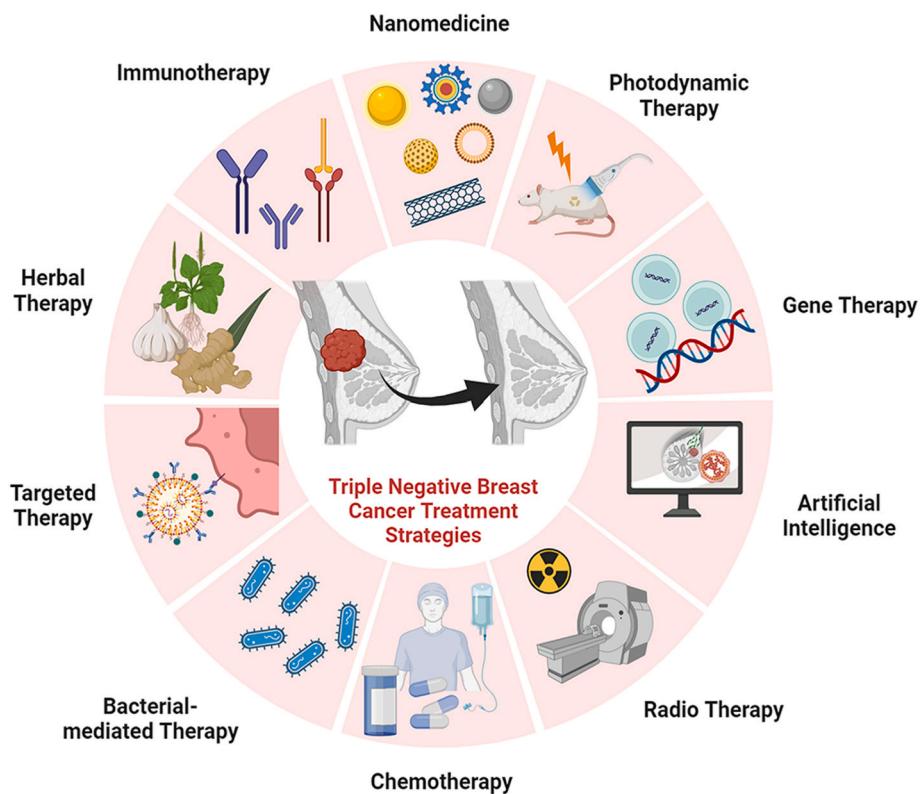


Fig. 3. Novel approaches for combating the drug resistance.

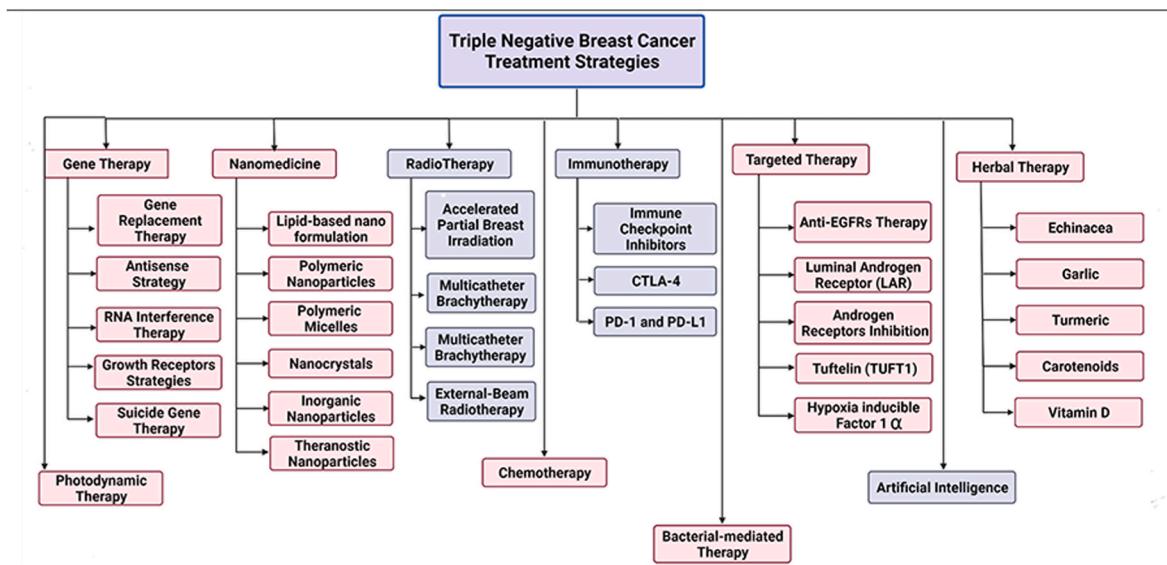


Fig. 4. Treatment strategies for the management of TNBC.

for the most. ATP-binding cassettes (ABCs) transporter and its subunits (eg. ABCC1/MRP1, ABCG2/BCRP, ABC11/MRP8) mainly involve drug resistance in several solid tumors, including BC.

Similarly, other agents or factors include Cancer stem cells, hypoxia, escaping of apoptosis, microRNAs, etc. Also enhance chemo-resistance [142]. Researchers reported Wnt ligands and TGF- β as the significant cause of propagation and chemoresistance against TNBCs [143,144]. Different Treatment strategies for the management of TNBC are shown in Figs. 3 and 4. Additionally, various types of delivery systems are discussed in Table 1.

4.1. Targeted therapy in cancer

The cancer cell is considered a dramatic cell since it can resist drugs given during treatment. The self-mutation tendency of these cells challenges scientists to target specific ligands and receptors to halt chemo-resistance for available drugs [128].

The Epidermal growth factor receptor (EGFR) is overexpressed in nearly half of cases of TNBCs or Inflammatory Breast Cancer (IBC). Studies proved that anti-EGFR therapy is a promising approach for reducing chemoresistance. Jin [145] provided excellent strategies for

Table 1

Drug delivery system for breast cancer treatment.

Therapy	Drugs/Ligands/antibodies	Formulations	Outcomes	References
siRNA-Mediated Gene Silencing	siRNA targeting cyclin-dependent kinase 1 (CDK-1)	Cationic lipid-assisted PEG-PLA nanoparticles	Promotion of cell death in c-myc overexpressed TNBC cells by inhibiting CDK-1 expression	[325]
	Aptamer-guided siRNA nanoparticles targeting CD-44	Core: siRNA-protamine complex, Shell: Aptamer ligand	Exhibited anti-tumor activity	[326]
	siRNA loaded into lipid-coated calcium phosphate nanoparticles	Lipid-coated calcium phosphate nanoparticles	Increased delivery of siRNA to TNBC cells	[327]
	Doxorubicin, Orlistat	Combination of Orlistat-loaded nanoparticles with doxorubicin/antisense-miR-21-loaded NPs	The combination increases in the apoptotic impact	[328]
Chemotherapy	Anthracyclines (e.g., doxorubicin)	Liposomal Intravenous administration	Tumor shrinkage, reduction in recurrence rates	[329]
	Docetaxel and Carboplatin	Intravenous administration	Determination of the pCR rate with docetaxel and carboplatin and to identify molecular alterations and/or immune gene signatures predicting pCR.	[330]
Sonodynamic Therapy	Nitrogen mustard, Cyclophosphamide, Bleomycin, Adriamycin	Sonosensitizer	Enhances the efficacy of chemotherapeutic agents using ultrasound waves	[331]
	Chlorin e6	Sonosensitizer: PEG-IR780@Ce6	Excellent performance in inhibiting cancer cells and in simultaneously suppressing the migration and invasion of cancer cells	[332]
	Doxorubicin	Deep-penetrating sonochemistry nanoplatform (Pp18-lipos@SRA737&DOX, PSDL)	Study portrays controlled production of reactive oxygen species (ROS) upon ultrasound activation and the resulting intercalation of DOX into the nucleus DNA and induction of apoptosis	[333]
	Manganese-protoporphyrin (MnP)	Folate-liposomes	The study shows that nano sonosensitizer, exhibited high acoustic sensitivity in deep tissue under ultrasound treatment, generating reactive oxygen species (ROS) suppressing both superficial and deep-seated tumor growth	[334]
Photothermal Therapy	IR820	PLGA nanoparticles	Induced cell death through apoptosis in TNBC	[335]
	Gold nanobipyramids	HA-coated nanoparticles (high and low MW HA)	Superior targeting of CD44 overexpressed TNBC cells	[336]
	Gold nanostar, siRNA	Gold nanostar, siRNA targeting CD44, reducing HSP72	Selectively sensitized TNBC cells to hyperthermia	[337]
Immunotherapy	Doxorubicin	Polydopamine nanoparticles loaded with JQ1 and PD-L1	Increased immune response through cytotoxic T-lymphocytes	[338]
	Bispecific Antibodies	Combination therapy with immune checkpoint inhibitors	Targeted TNBC cells and combination therapy with immune checkpoint inhibitors	[339]
	Curcumin analogue	HA-SMA-TPGS nanomicelles	Targeted CD44-mediated apoptosis pathway in TNBC	[340]
Photodynamic therapy	PD-1/PD-L1 inhibitors	Anti-PD-1 antibodies, anti-PD-L1 therapeutic antibodies	Activated anti-tumor immune responses by blocking immune regulatory checkpoints	[341,342]
	Tremelimumab, Ipilimumab	CTLA-4 inhibitors	Activated T-cell-dependent immune response	[343]
	Indocyanine green (ICG)	Thermosensitive liposomes	Successful accumulation in tumor cells	[344]
Targeted therapy	Cationic porphyrin, HIF-1 alpha siRNA	Multifunctional cationic porphyrin grafted microbubble	Effective treatment of TNBC using ultrasound targeted PDT	[345]
	VEGF inhibitor (siRNA)	Biocompatible copolymer nanocomplex	Inhibited migration and invasion of TNBC cells, high tumor penetration and cellular uptake	[346]
	VEGF inhibitor (siRNA): Paclitaxel	DEAE-Dextran coated paclitaxel nanoparticles	Maximum cellular uptake, downregulated intratumoural VEGF protein levels, and strong anti-tumor activity	[347]
	EGFR inhibitors: Doxorubicin, Docetaxel	Gefitinib, Cetuximab, PEGylated nanomedicine (PEG-liposomal doxorubicin), Docetaxel-loaded PEG-PCL nanoparticles	Targeted EGFR, inhibition of cell proliferation and DNA repair, improved anti-proliferative activity	[348, 349], [350,351]
	PARP inhibitors: Olaparib, Veliparib, Niraparib, Rucaparib, Talizumab	Olaparib, Veliparib, Niraparib, Rucaparib, Talizumab	Promising results in BRCA-mutated TNBC, improved immune responses, reprogramming glucose and lipid metabolism	[352]
	mTOR inhibitors	Ipatasertib, Capivasertib, Combination with paclitaxel, CDK4/6 inhibitors	Enhanced efficacy, improved progression-free survival, manageable adverse effects	[353,354]

combating drug resistance for TBNCs. EGFR has an ongoing mechanism with Insulin-like growth factor 1 type (IGF-IR). The resistance of anti-EGFR agent gefitinib is confirmed by increased PI₃K and Akt activity, which is directly associated with IGF-IR. Further, Non-receptor tyrosine kinases such as Src, show excellent activity through tamoxifen/gefitinib resistance BC [146].

The presence of Luminal androgen receptor (LAR) in breast cancer shows necessary particulars for DRs. Androgen receptors (AR) and Luminal Expression layouts are the primary identification parameters for detecting LAR. Similarly, PI₃K/Akt/mTOR pathways activated by the Phosphoinositol 3 Kinase CA (PI₃KCA) mutations also sum up for resistance to chemotherapeutic agents. Inhibiting Androgen receptors can directly suppress LAR ultimately it decreases chemical resistance

[147].

Liu proved that Tuftelin (TUFT1), a protein, is also directly responsible for chemoresistance associated with TNBCs [148]. The chemoresistance studies were done on shTUFT1—MDA-MB-231 cells, and it was seen that TUFT1 was overexpressed in the TNBC xenograft tumor model. Semaphorin-3F, modulator, and RAc1 inhibitor indirectly inhibit the expression of TUFT1 protein, which ultimately reduces drug resistance [149].

Evidence also claimed that Hypoxia-inducible factor 1α (HIF-1α) equally contributed to progression and metastasis associated with docetaxel resistance by reducing the miR-494 expression/survivin signaling pathway. HIF-1α can be easily targeted by using PX-478, an antagonist that either reduces protein expression and lead to

degradation [150,151]. Scialla et al., developed the targeted theranostic nanoformulation for the treatment of TNBC. The formulation was composed of iron oxide NPs and doxorubicin. Conducting in vitro investigations, we employed the J774A. One macrophage cell line at pH levels of 7.4 and 6.5 to confirm the pH-responsive targeting ability towards tumor-associated macrophages (TAMs). To demonstrate the viability and efficacy of the refined targeted formulations, both the MDA-MB-231 TNBC cell line and an animal model harboring M-Wnt tumors were utilized. The lipid nanovehicles loaded with DOX exhibited a selective accumulation within the tumors of M-Wnt tumor-bearing mice. This led to a potent inhibition of tumor growth while significantly mitigating off-target damage compared to free DOX, showcasing promising results for targeted therapy [152].

4.2. Gene therapy

Gene therapy is a technique of curing and preventing disease by addressing the cause at its genetic level. Rather than relying on pharmaceuticals or invasive procedures, doctors can now use gene therapy to modify a patient's genetic composition in order to alleviate their condition. There has been a dramatic transition from the theoretical realm of works to the practical and therapeutic area of cancer gene therapy, notably in the management of TNBC [153]. While current treatments for breast cancer encompass chemotherapy, radiation therapy, surgery, hormone therapy, and laser therapy, these methods come with inherent risks and adverse effects for patients [154]. In contrast, gene therapy uses molecular techniques that significantly reduce patients' exposure to potentially harmful substances while providing all the benefits of conventional treatment. Gene therapy was first introduced in 1980 by Martin Cline to modify human DNA. In May 1989, the first NIH-approved nuclear gene transfer was successfully carried out in humans. In a trial beginning in September 1990, French Anderson used gene transfer for the first time for therapeutic purposes. This was also the first time human DNA had been inserted directly into the nuclear genome. In the long run, it may be able to correct or perhaps reverse many hereditary problems [155]. Lui et al., designed the hypoxia-responsive polymeric micelles loaded with doxorubicin and shHIF-1 α . Results showed within a mouse model simulating orthotopic TNBC, the concurrent utilization of chemotherapy and gene therapy targeting HIF-1 effectively inhibited the primary tumor's growth and the emergence of distant metastases. The notable biocompatibility and sensitivity to hypoxia of hypoxia-responsive polymeric micelles have positioned them as a promising avenue for delivering medications and genes, holding significant potential for treating TNBC and other tumors thriving in hypoxic conditions [156]. Gene therapy consists of different techniques such as:

Gene replacement therapy in this therapy, tumor suppressor gene (TSG) replacement, is a promising strategy in gene therapy for TNBC. Cancer development may occur when one or more TSG genes are missing. TSGs may induce either tumor cell suppression or death. Gatekeeper genes are inactive gene that activate only in the presence of the cancerous cell and can halt the cell cycle. Some of these gene are including BRCA1, BRCA2, p53, Rb, p16, p27, p21, Testin, Maspin, and melanoma differentiation-associated gene-7 (mda7) [157]. TSGs, such as p53, were found to be the targets of most replacement strategies in clinical studies. This approach aims to reestablish the natural balance between cell growth and cell death in cancer cells by introducing the expression of wild-type p53 into these cells. One facet of p53 insertion is the bystander effect. This indicates that a tiny fraction of transduced *in-vivo* cancer cells undergo a double-stranded DNA break, killing out both the transduced and non-transduced cells around them when p53 is introduced. Proposed processes include the production of soluble pro-apoptotic proteins, activating the immune system, and antiangiogenesis. A bystander effect is advantageous for effective gene therapy strategies [158]. Zhang et al., In 1994, researchers reported the first effective delivery of p53 to lung cancer using adenoviral vectors. Consequently, an

in-vivo investigation of breast cancer p53 gene transfer xenograft models was conducted [159]. The rb gene is the second potential TSG for replacement therapy in TNBC. Registered clinical studies include p53, Rb, and md7 genes in TSG gene replacement therapy for TNBC [160].

Antisense strategy in this method, it's possible that antisense chemicals may stop dangerous genes from being expressed. Small molecules of single-stranded DNA (ssDNA) called antisense oligonucleotides alter the regulation of genes by blocking the translation of DNA into protein [161]. The most effective antisense method involves substituting sulfur for one of the oxygen atoms in the phosphodiester bond. In fact, this backbone change improves oligomer stability and nuclease resistance. Studies on antisense suppression of oncogene activity showed that c-MYC treated with bare antisense DNA might stop lymphoma growth. Other TNBC-related genes that antisense oligonucleotides have successfully targeted include telomerase, telomerase reverse transcriptase, plasma membrane calcium ATPase, erythroblastic oncogene B homolog 2 (c-erbB-2), p21, B-cell lymphoma 2 (Bcl-2), cellular oncogene fos (c-fos), erythroblastic oncogene B homo (IGF-IR) [162].

RNA interference therapy RNA interference (RNAi) technology is also another useful approach for gene therapy. It is a possible intracellular mechanism that can turn off genes after they have been written down. It starts with double-stranded RNAs (dsRNA) that are the same as the genes [163,164]. This method for either short-term or long-term suppression of the target gene's expression in TNBC may be used using siRNA and short hairpin RNA (shRNA). Accordingly, several investigations showed that downregulating c-specifically through RNA interference, prevents the growth of breast cancer MCF-7 cells both *in vitro* and *in vivo* [165]. Ribozymes are a different method for eliminating oncogenes in breast cancer. These RNA molecules can function as enzymes even when no proteins are present. Additionally, they may stimulate the creation of covalent bonds in RNA strands at certain places and the cleavage of RNA substrates [166]. Human immunodeficiency virus (HIV) infection was the first condition for which ribozymes were used as a treatment [167].

Growth receptor strategies: This method employs the extensively studied protooncogene erbB-2 to interfere with the standard cellular location of growth receptors. Therefore, transduction of a gene producing an anti-erbB-2 intracellular single-chain antibody (sFv) may reduce cell surface erbB-2 levels and induce death in erbB-2 overexpressing breast cancer cells.

Suicide gene therapy This therapy was introduced in 1980 [157]. In this therapy genes injecting into the enzyme or protein that causes tumor cells to self-destruct. This method is classified into toxin-based gene therapy and gene-directed enzyme prodrug therapy (GDEPT) [168].

Transferring genes to enable the production of toxins is referred to as toxin gene therapy, whereas the transfer of genes to facilitate the expression of enzymes that selectively activate specific prodrugs is known as enzyme-activating prodrug treatment. GDEPT is advantageous because it improves the effectiveness and safety of traditional cancer chemotherapies. This method is categorized as a two-phase gene therapy strategy for cancer treatment [169]. Stage one involves introducing the gene for an exogenous enzyme to breast cancer cells. Step two involves providing a non-toxic prodrug that, once produced by the foreign enzyme within the tumor, becomes a cytotoxic active form. The same holds for transfected breast cancer cells, which active prodrugs may destroy. GDEPT-indicated enzymes in breast cancer may be split into two categories [170]. Carboxypeptidase G2 (CPG2), cytosine deaminase (CD) from bacteria, and thymidine kinase (TK) from viruses all fall into the first class of nonmammalian enzymes. In contrast, human enzymes belong to a separate second group, including cytochrome P450 isoforms. CD and TK are crucial examples in this context, as they play significant roles in activating 5-fluorocytosine and ganciclovir (GCV), respectively, leading to their conversion into potentially hazardous medication forms [171].

4.3. Bacterial-mediated therapy

Busch and Fehleisen discovered a connection between tumor and bacteria, describing a case in which infection with *Streptococcus pyogenes* caused erysipelas and subsequently slowed the development of the patient's tumor [172]. During the 1890s, William Coley was the first to employ a *Streptococcus* and *Serratia marcescens* attenuated bacterial combination for treating tumors. Coley's toxin was the name given to this compound [173]. As a result, researchers began looking for and testing bacterial strains and their products to combat cancer [174]. A wide range of tumors, such as leukemia, lymphoma, melanoma, and solid carcinomas, may be treated using bacterial-mediated treatment. Today, genetically engineered microorganisms are usually employed for this purpose, and bacteria allow for various approaches to cancer treatment [175]. The production of gene transfer, tumor-specific antigens, pro-drug cleavage and RNA interference are just a few of the many methods that have been developed to combat cancer [176]. Infesting low-antigenic tumors with specific facultative or obligate anaerobic bacteria increases bacterial concentration and proliferation. Consequently, antitumor immune responses become more active, leading to accelerated tumor destruction. This process involves manipulating various resistant system components, including CD4⁺ and CD8⁺ T cells, Tregs, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). Additionally, researchers have observed that certain conserved bacterial ligands act as agonists for receptors in the innate immune system, such as toll-like receptors (TLR). Binding of these ligands to the receptors triggers an intracellular signaling cascade, resulting in the production of proinflammatory cytokines. In addition, certain bacterial components, such as exotoxins, have been shown to begin anticancer activities by acting directly on tumor cells, as opposed to acting indirectly [172]. Using bacteria as a vector for delivering therapeutically relevant transgenes offers several advantages. These bacteria, such as *Clostridium*, flourish and move freely in the anaerobic/hypoxic environment commonly found in tumor cells. Among the frequently employed bacteria for breast cancer vaccines are *Salmonella typhimurium*, *Listeria monocytogenes*, *Clostridium novyi*, *Clostridium acetobutylicum*, *Bifidobacterium longum*, *Bifidobacterium adolescentis*, and *Escherichia coli* [177,178]. Tumor treatment using bacteria can be classified into two; (1) oncolysis or (2) addition of the cytotoxic/desired gene into tumor cell [179]. Yamada et al., discovered bacterial strains to generate redox proteins that destroy tumor cells by triggering programmed cell death and cell cycle arrest in MCF-7 cells. *Pseudomonas aeruginosa*'s Azurin protein kills cancer cells by interrupting the cell cycle and inducing apoptosis via the production of p53 and Bax, preventing the growth of TNBC and halting its spread [180].

Li et al., prepared a therapeutic platform centered around bacterial outer membrane vesicles (OMVs) for the management of TNBC. These modified OMVs have shown potential as immune-stimulating agents, enhancing antitumor immunity. However, the limited therapeutic window of free OMVs has hindered their widespread use. To address this, the author loaded OMVs into macrophages and explored their potential for co-delivering Ce6 and DOX, enabling combinational tumor photodynamic/chemo-/immunotherapy. The OMVs exhibited a particle size of 70–140 nm with a polydispersed index of 0.234, and *in-vivo* antitumor effectiveness demonstrated that macrophages produced them effectively. Which would subsequently be taken up by neighboring cells in the tumor microenvironment, resulting in synergistic anticancer effects. Although the released chemotherapeutics may cause harm to the vehicle macrophages, the immunostimulatory action of OMVs would ultimately lead to more potent antitumor responses. Mice with tumors whose weight was reduced by OMV treatments quickly regained lost weight. Furthermore, as 4T1 tumors were significantly metastatic to the lung, we analyzed lung metastasis in treated mice. Biodistribution data indicated that Ce6/DOX-OMVs@M accumulated in the liver; hence its hepatotoxicity was tested. Because of this, no abnormal alterations were seen in the H&E staining of the liver tissue, and the ALT and AST values

in the blood were within normal limits. Treatment with Ce6/DOX-OMVs@M had no discernible effect on kidney function, as measured by blood levels of BUN and Cr. *In vitro*, hemolysis assays demonstrated that i. v. Administration of Ce6/DOX-OMVs@M would not cause hemolysis, indicating that the compound is harmless to RBCs [181].

Ganai et al., reported the tumor targeting using the *Salmonella typhimurium*. The author used the bacterial radiation-inducible RecA promoter to create a non-pathogenic *S. Typhimurium* to release murine TNF-related apoptosis-inducing ligand (TRAIL). Results showed Irradiation TRAIL secretion from modified *S. Typhimurium*, which leads to caspase-3-mediated cell death and death in 4T1 mammary cancer cells in culture. Salmonella systemic injection coupled with TRAIL expression upregulation by 2Gy g-irradiation significantly slowed the progression of breast tumors and lowered the probability of mortality by 76% compared to irradiated controls. The 30-day survival rate went from zero to one hundred percent after repeated doses with TRAIL-bearing Salmonella combined with radiation [182]. Yazawa et al., systemically applied non-pathogenic and anaerobic microorganisms *Bifidobacterium longum* localized specifically to and flourished in 7,12-dimethylbenz [a] anthracene-induced rat mammary tumors. After the examination of the rat the bacteria were detected only in tumor tissue and not detected in the normal tissues, including the liver, spleen, kidney, and lung. The author found that gene therapy of solid tumors might benefit from this innovative method to tumor targeting utilizing *Bifidobacteria* [183]. L et al., conducted the study to examine the efficacy of *Clostridium perfringens* enterotoxin (CPE)-mediated treatment in treating breast cancer, and looked into CLDN 3 and 4 expression. Overexpression of CLDN 3 and 4 in comparison to normal mammary epithelial tissue was seen in roughly 62% and 26% of primary breast carcinomas, respectively (n = 21). When CPE was added to cultured breast cancer cell lines, only the cells that expressed CLDN 3 and 4 were killed quickly and dose-dependently. Tumor volume was significantly reduced (P < 0.007), and necrosis was seen after intra-tumoral CPE treatment of xenografts of T47D cancer cells in immunodeficient mice [184]. Ei-atti et al., discussed the application of probiotics in managing chemotherapy-induced diarrhea in this case study. The authors discuss the experience of a stage IV breast cancer patient who found relief from diarrhea through the use of a probiotic blend containing various species [185]. Hu et al., synthesized the doxorubicin NPs with the surface modified with alized bacteria (*Bifidobacterium bifidum*). The *in-vivo* results showed that the developed NPs prolonged the survival rate and significantly inhibited tumor progression and metastasis [186].

4.4. Nanomedicine

Patients with TNBC are typically given a combination of mainstream treatments (chemotherapy, surgery, radiotherapy) and alternative therapies (acupuncture, nutritional counselling, etc.). Radiation therapy and surgical removal of the breast tumor are the two most common approaches to dealing with this kind of cancer. They become less useful as the cancer spreads [187]. Here, focusing on the medication treatment, which is the last of the modalities, since it may diminish the tumor load and help stop, slow, or reverse cancer's spread to other organs. The last twenty years have seen significant developments in nanotechnology, which may one day lead to novel approaches to treating various ailments. The development of nanotechnology-based contrast substance and drug delivery carriers for detecting and managing illness is moving toward greater specificity and efficacy [188]. Drug delivery systems based on nanoparticles (NPs) can potentially improve treatment efficacy with fewer side effects, pharmacokinetics, encapsulation of the drug, and tumor deposition burden via the EPR effect.

Furthermore, tumor selectivity and drug distribution in cancer cells may be improved by binding active target ligands to particle surfaces [189]. To overcome the difficulty inherent in getting NPs to their intended human tissue sites, researchers have come up with several solutions, including designing nanoparticles with improved

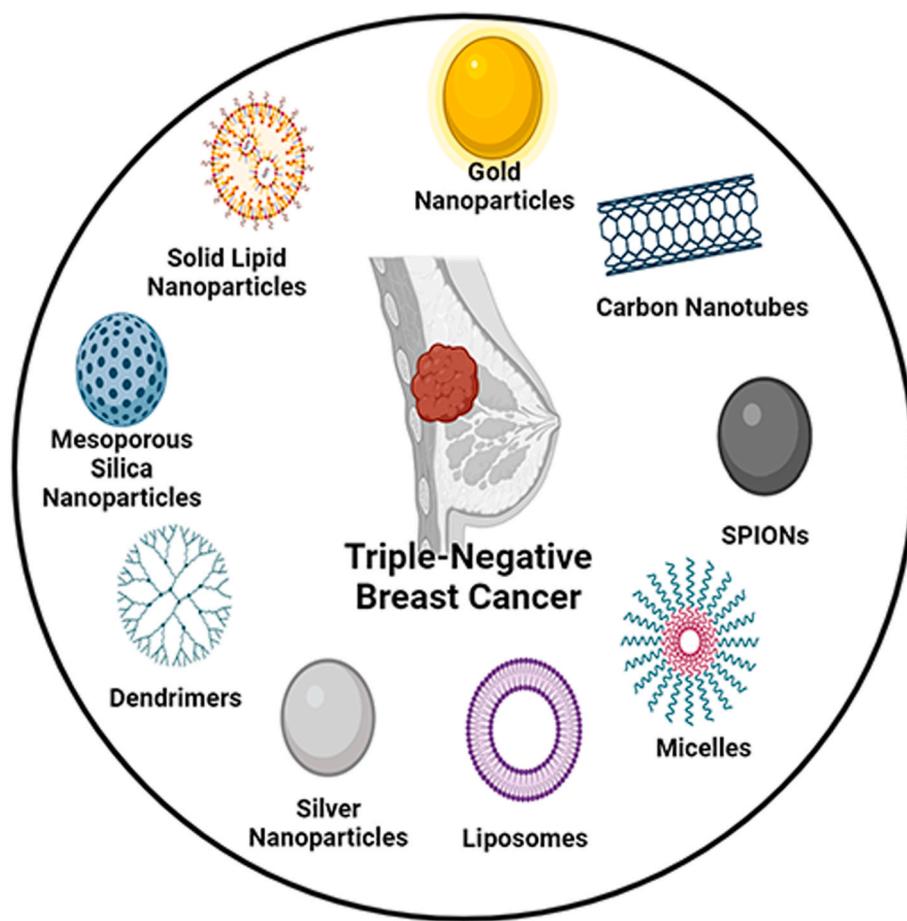


Fig. 5. Nanomedicine for combating the drug resistance.

pharmacokinetic properties and a multistage delivery system, as well as increasing EPR effects through the application of X-ray radiation and high-intensity focused ultrasound (HIFU) [190]. Nanocarriers, such as NPs/tubes [191], micelles/dendrimers, and liposomes, are now made up mostly of polymers, metals, lipids, nucleic acids, and proteins. Different types of nano formulations for treating TNBC are shown in Fig. 5.

4.4.1. Lipid-based nano formulation

Lipid-based formulations have demonstrated the greatest success among the numerous nanoformulations utilized in cancer treatment. Several lipid-based formulations, such as liposomal systems, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC), are currently in use.

Chaudhuri et al. discussed the lipid-based nanoparticle for the management of TNBC. The author addressed many therapeutic benefits over traditional treatment and other nanoparticles, such as higher loading capacity, improved temporal and thermal stability, reduced therapeutic dosage and related toxicity, and minimal drug resistance. Furthermore, LNPs transcend physiological barriers, enhancing therapeutic accumulation at the target region [192].

Liu et al., used gene therapy with the combination of lipid-based nanoparticles to manage TNBC. Targeted lipid-protamine-DNA (LPD) nanoparticles are employed to deliver the C-C motif chemokine ligand 2 (CCL2) trap plasmid DNA (pCCL2) to the tumor microenvironment (TME). This localized expression of the CCL2 trap aims to alleviate the immunosuppressive effects of the TME. This method significantly outperforms the currently available CCL2 antibody regarding therapeutic effectiveness and tumor growth suppression in murine TNBC 4T1 cells [193].

Yan et al. discussed the lipid-based NPs decorated with siRNA for

treating BC. This approach attracts researchers because of its unique properties to target the tumor and protect the siRNA [194].

4.4.2. Liposomal based nanocarrier

In nanoformulation, liposomes are most typically utilized for medication delivery. Lipoproteins have a bilayer structure made of phospholipids and cholesterol, which are biocompatible and biodegradable. The bilayer-structured phospholipids improve the solubility and stability of anticancer medicines [195]. Additionally, cholesterol enhances the stability of NPs in blood, increases the penetrability of lipophilic drugs across the lipid bilayer, and decreases the mobility of NPs. They're used to load both hydrophobic and hydrophilic medications [196]. The U.S. FDA has approved liposomal drug delivery. Targeted liposomes have been produced to deliver medicines to the cancer cell or tumor microenvironment with the least amount of non-specific distribution in healthy tissues or organs. The first chemotherapy nano system utilized therapeutically is Doxil, a liposome containing doxorubicin (DOX). The PEGylated liposomal formulation of Doxorubicin reduces blood levels without compromising the drug's anticancer properties. This is achieved by prolonging the circulation time of the nanoformulation and preventing its early clearance [197]. Li et al., reported the targeted liposomal nanocarrier of different anticancer drugs for the management of TNBC. IC₅₀ value of anticancer agents such as mertansine, paclitaxel, gemcitabine, and DOX were tested in the TNBC cell lines MDA-MB-231 and MDA-MB-468. The study of the cell lines revealed that the developed targeted liposomal nanocarrier inhibits tumor growth [196]. Dong et al., reported the epalrestat and doxorubicin dual-loaded liposomal nanoformulation for treating TNBC. Hyaluronic acid is used as a targeting agent at the CD44 receptor. The formulation releases both drugs simultaneously to the tumor environment, which suppresses the tumor

growth and epithelial-mesenchymal transition [198].

Duarte et al., prepared a pH-sensitive liposomal formulation by co-encapsulating DOX and simvastatin (SIM). The study evaluated the effect of these medication combinations, at molar ratios of 1:1, 1:2, and 2:1, on three human breast cancer cell lines: MDA-MB-231, MCF-7, and SK-BR-3. Both free drugs and the drugs co-encapsulated into pH-sensitive liposomes were assessed in the study. The formulations had a polydispersity index (PDI) of less than 0.3 and a size of less than 200 nm. DOX to SIM had encapsulation contents of around 100% and 70%, respectively. DOX: SIM molar ratios of 2:1 were shown to have a more significant inhibitory impact on breast cancer cell lines when using free and encapsulated drugs [199].

4.4.3. Solid lipid nanocarrier

Lipid-based colloidal medicinal drug delivery systems, known as solid lipid nanoparticles (SLNs), are nontoxic and biodegradable. In the early 1990s, a polymer-based alternate delivery system became recognized. Most often, SLNs are used to improve the oral bioavailability of less water-soluble drugs. They offer various benefits, including simple manufacture, pharmaceutical stability, improved drug entrapment, effective *in-vitro* drug release, and long-term stability [200]. Multiple investigations have shown that SLNs may either solubilize lipophilic chemotherapeutics uniformly inside the lipidic matrix or form a drug-rich shell encircling the lipidic core. Moreover, depending on the drug accumulation pattern inside the lipid matrices, i.e., chemotherapeutics-enriched core or chemotherapeutics-enriched shell, the drug release profile may be managed to our benefit to meet the required release profile [192]. Rocha et al., developed the docetaxel encapsulate SLN for managing lung and mammary carcinoma. The high-energy approach was used to create SLNs. The lipid matrix Compritol 888 ATO was utilized to formulate the SLNs. The surfactants Pluronic F127 and Span 80 were employed to stabilize the dispersion of the SLNs. Notably, there was minimal change in particle stability observed over a period of at least 120 days. The polydispersity index (PDI) for the SLNs was 0.2, and both the particle size and zeta potential showed negative values. With a drug loading of only 2%, the SLNs demonstrated an impressive 86% effectiveness in entrapping docetaxel (DTX). The IC₅₀ of SLN-DTX was over a factor of 100 lower than that of free DTX when tested on 4T1 cells. In the cellular uptake test, SLN-DTX was substantially more efficiently taken up by cells than free DTX. SLN-DTX (73.7%) accumulated in the G2-M phase, which was much greater in the cells than in the free DTX alone (23%). It showed apoptosis [201]. Zheng et al., developed the DOX-loaded arginine-glycine-aspartic (RGD) tripeptide-modified pH-sensitive SLN. To investigate the anti-tumor activity of RGD-DOX-SLNs, cancer cell lines (MCF-7) and DOX-resistant cell lines (MCF-7/ADR) were used. The particle size and zeta potential of developed NPs were 93.3 nm and 35.6 mV. Terminal half-life (T_{1/2}) and maximum drug concentration (C_{max}) were 10.58 h and 39.12 ± 2.71 L/kg/h [195]. Hatami et al., prepared the quercetin-loaded SLN for the treatment BC by β-catenin pathway. The results revealed that the quercetin-SLN exhibited the most favorable characteristics, boasting a particle size of 154 nm, a zeta potential of -27.7 mV, and an impressive encapsulation efficacy of 99.6%. Compared to quercetin alone, the application of quercetin-SLN notably decreased cell viability, migration, sphere formation, and the expression of key proteins β-catenin and p-Smad 2 and 3. Moreover, gene expressions of CD44, zinc finger E-box binding homeobox 1 (ZEB1), and vimentin were substantially reduced, while gene expression of E-cadherin witnessed a noteworthy increase [202].

4.4.4. Nanostructured lipid carriers

Nanostructured lipid carriers (NLCs) represent the second generation of lipid nanoparticles, consisting of a hybrid blend of solid and liquid (oil) lipids. The unique combination of these lipids allows the NLC matrix to remain solid at body temperature while maintaining a melting point below that of the SLNs. This property enhances the stability and

performance of NLCs as drug delivery carriers. These characteristics may manage SLN particle issues such as storage, distribution, and medication limiting. All developed NLCs aim to improve active ingredient delivery and prevent medication leakage by creating a specific structure in the lipid matrix during storage [203]. SLNs with these advantages show potential for the delivery of anticancer agents. The delivery of anti-cancer agents to cancer cells more precisely means that normal cells are less impacted and will thus have fewer side effects. On the other side, there might be more drug concentration closest to the cancerous cells, meaning that lower drug dosages would be sufficient and resistant cells would be eliminated, decreasing the need for larger drug doses and the likelihood of resistance [204]. Borges et al., developed the doxorubicin and sclareol encapsulated NLC to manage TNBC. The developed formulation was tested for the *in-vitro* parameters, and cell-line studies were conducted on the MDA-MB-231 and 4T1 cells. Both drugs showed synergy at the molar ratio of DOX:SC (1:7.5) *in-vitro*. Dual drugs loaded NLCs showed good efficacy for the breast cancer treatment in mice and histopathological study reviled no toxicity of the formation to the organ [205]. Varshosaz et al., developed DTX-loaded NLCs modified with trastuzumab (The results demonstrated that the stearyl amine-loaded NLCs had the smallest particle size, the most significant zeta potential, and the highest antibody coupling efficiency values. Zeta potential and drug entrapment effectiveness were decreased due to Herceptin binding to NLCs, whereas particle size rose. Spermine-containing NLCs released DTX more slowly than those containing other fatty amines for the management of HER2-positive breast cancer. The efficacy of the developed formulation was evaluated on the MDA-MB-468 (HER2 negative receptor) and BT-474 (HER2 positive) breast cancer cell lines. Cell line studies revealed the excellent efficacy of the NLCs for the selected cell. Flow cytometry studies showed that the BT-474 cells more readily absorbed nanoparticles chemically attached to Herceptin [206]. Ersoz et al., prepared doxorubicin and gold NPs loaded in NLCs. The results showed cytotoxic effect of prepared NPs on the MDA-MB-231 BC cells and tumor growth inhibition was found to be 81%. The investigation revealed that the geometry of AuNPs directly influences their photothermal capabilities. The synergistic interplay between the cytotoxic effects of DOX and the localized hyperthermia induced by AuNPs greatly amplifies their ability to cause irreversible cellular damage. These advanced formulations exhibit substantial potential as highly effective agents for combined cancer therapy [207].

4.4.5. Polymeric nanoparticles

It consists of chemotherapeutic agent-loaded nanosized particles that are biocompatible and biodegradable (encapsulated or, entrapped or conjugated) [208,209]. NPs are classified as nanospheres or nanocapsules, depending on how the medicine is contained. Due to the physical characteristics of the polymer, NPs delivery at targets has many advantages over conventional colloidal systems, including reduced toxicity, longer circulation period leading to health benefits, improved cell absorption, biocompatibility, organ distribution uniformity, and EPR effect. These different properties of polymeric nanoparticle claims make it a good option for effectively managing TNBC [210]. Almoustafa et al., developed the DOX-loaded surface coated with hyaluronic acid polymeric NPs to manage TNBC metastasis. The *in-vivo* studies outcomes reveled that hyaluronic acid-coated NPs decrease tumor growth. According to fluorescence microscopy, metastasis in the liver, spleen, colon, and lungs was considerably ($p < 0.05$) lower in the HA-PEG-PLGA NPs group compared to the control and Free DOX groups [211]. Akram et al., reported the tumor micro-environment sensitive chitosan-based doxorubicin polymeric nanoparticle. The particle size of the NPs was 175 nm. The XRD confirmed the amorphous nature, and the thermal stability of the sample was 100 °C. It was determined whether or not the pH of the tumor location affected the release of doxorubicin from the PNPs. In a study utilizing a UV-Vis Spectrophotometer, the encapsulation efficacy of PNPs for the chemotherapy doxorubicin was calculated to be 89% (4.45 mg/5 mg). At a pH of 5.3, drug release from PNPs was

88% (3.92 mg/4.45 mg) after 96 h. Different PNPs with varied concentrations of DPA may be utilized to deliver chemotherapeutic drugs [211] efficiently.

4.4.6. Polymeric micelles

Hydrophobic bases for water-insoluble and hydrophilic shells meant to load water-soluble drug molecules make polymeric micelles (PMs) a promising drug delivery method. Hydrophilic encapsulation provides nanostructured micelles with structural integrity [212]. Micelles of the nanometric size are well suited for the administration of water-soluble anti-cancer drugs because they can sustain a large payload, a prolonged retention period in the circulation, an improved permeability to the drug, a powerful penetration of the tumor, and an even dispersion of the medication. The biological stability of polymeric micelles has been improved, and new developments in polymeric micelles design show that drug delivery systems may be created to specifically target certain tissues. Various strategies are available in micelles for targeting TNBC: conventional PMs, pH-responsive PMs, redox-responsive PMs, temperature-responsive PMs, magnetism-responsive, and enzyme-responsive PMs [213]. Lim et al., fabricate the PMs encapsulated with paclitaxel and CSF1R inhibitors to manage TNBC. The findings show that large doses of PTX in POx, even when used alone, have profound effects on TME and trigger the formation of permanent immunological memories. Authors further show that repolarization of the immunosuppressive tumor microenvironment (TME) and an increased T cell immune response decrease primary tumor progress and metastasis when used together in a variety of TNBC models, yielding consistent treatment benefit [214]. Lim et al., developed the spherical and worm-like PMs to manage TNBC. Poly (2-oxazoline)-based polymeric micelles have been shown to undergo elongation from a spherical to a worm-like form over time, with elongation regulated by several factors such as the quantity and kind of medication injected into the micelles. Micelles with a spherical shape aggregate quickly in tumor tissue while retaining considerable doses of medication; micelles with a worm-like shape collect more slowly and only after releasing significant amounts of drug. The results showed the importance of the PMs for effectively delivering anticancer agents to the target sites [215]. Zuo et al., developed the halofuginone-loaded TPGS PMs to manage TNBC. The findings showed that HTPM was stable and released steadily in the model GI fluids. Since HF was shown to be a P-glycoprotein (P-gp) substrate, encapsulation in TPGS polymeric micelles significantly improved its permeability across Caco-2 cell monolayers by increasing intracellular uptake and suppressing P-gp efflux. When taken orally, HTPM had more tumor-suppressing effects than HF alone in subcutaneous xenografts of MDA-MB-231 cells. While HF alone caused weight loss and jejunal hemorrhage in the studied animals, oral administration of HTPM at the therapeutic dosage did not produce any pathological harm [216]. Lim et al. developed PMs containing paclitaxel and CSF1R inhibitors. The findings underscore that administering high-dose PTX via POx formulation exerts potent effects on the tumor microenvironment (TME) and fosters enduring immune memory, even when used as a standalone treatment. Moreover, our study illustrates that combining PTX and PLX3397 consistently enhances therapeutic outcomes across diverse TNBC models. This improvement arises from the repolarization of the immunosuppressive TME and an augmented T cell immune response, culminating in the suppression of both primary tumor growth and metastasis. In essence, this research underscores the significance of medication reformulation and introduces a promising translational strategy for PTX monotherapy and the PTX plus PLX3397 combination therapy, thereby advancing the potential treatment of TNBC through the utilization of POX polymeric micelles [217].

4.4.7. Nanocrystals

Nanocrystals are considered nano-sized pure drug particles shielded by a little number of surfactants. Nanocrystal is practical for water drug delivery, with promising industrialization and desirable drug loading

[218]. US-FDA has permitted the use of nine different nanocrystal-based products in human trials. Drug nanocrystals, in studies conducted in the lab, showed improved oral and systemic anticancer properties [219]. Zhao et al., developed the thermosensitive nanocrystals loaded with paclitaxel and niclosamide to manage TNBC. The developed nanocrystals were loaded in the PLGA_PEG_PLGA thermosensitive hydrogel. The optimal particle size and high drug loading were achieved in the optimized formulation. The drug release from PN-NCs-Ts Gel was stable for up to 8 days in vitro. Synergistic effects of combination treatment in reducing cell proliferation and migration and causing programmed cell death were reported in *in-vitro* anticancer testing. The combination treatment demonstrated the expected level of safety and an *in vivo* tumor growth inhibition rate of around 68% [220].

4.4.8. Inorganic nanoparticles

Many recent studies have revealed the potential of inorganic NPs for use in cancer detection and therapy. Better therapeutic effectiveness and decreased side effects may be achieved by using inorganic NPs as drug carriers owing to the simplicity with which targeting molecules can be modified, the rate of drug release can be regulated using a variety of stimuli, and the NPs can be targeted for delivery [221]. There are four main kinds of metallic nanoparticles: metal-ion NPs, metal oxide NPs, metal sulphide NPs, and bimetallic NPs. Metals used in various NPs, such as magnesium (Mg), gold (Au), copper (Cu), titanium (Ti), silver (Ag), zinc (Zn), and platinum (Pt) make up the first category of nanomaterials. Recent imaging and detection methods, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), may benefit from using inorganic NPs. Benefits of using inorganic nanoparticles for breast cancer include increased permeation and accumulation in malignant tissue, light absorbance, and surface plasma resonance in the near-infrared, radiation interaction leading to the generation of secondary electrons, and the capability to be conjugated with drugs or other agents. Gold (Au NPs) and silver (Ag NPs) are the most studied metallic nanoparticles for biomedical activities such as cancer treatment, diagnostics, and medication delivery [222]. It has been shown that gold NPs (AuNPs) are the most studied and promising metal NPs known to transport paclitaxel, a well-known anti-cancer medication. Differently shaped and fabricated Au NPs, such as Au-nanoshells (AuNS), Au-nanorods (AuNR), and Au-nanocages (AuNC), are emerging as a versatile nanovehicle for cancer treatment. PEG-coated Au NP and ionizing radiation improved survival in a mouse model of TNBC [223]. Serum-coated AuNR can potentially suppress gene expression in cellular energy production. In conclusion, cancer cells having less energy and being unable to migrate leads to invasion both *in vitro* and *in vivo* [224]. Antimicrobial and cytotoxic characteristics of silver NPs (AgNPs) have led to their broad use for treating a wide variety of cancers, including those of the breast, ovary, colon, brain, liver, and blood [225]. According to Swanner et al., AgNPs are taken up by both TNBC and nonmalignant breast cells, however, due to their fast breakdown in cancer cells, AgNPs are particularly harmful for TNBC cells. But, healthy cells were not affected by them [226]. After AgNPs were taken up by cells, the endoplasmic reticulum of TNBC cells was stressed owing to the increased production of cellular antioxidants. Still, the endoplasmic reticulum of normal cells was not negatively affected. To combat cancer, ZnO NPs may be used similarly to genotoxic medicines. Micronuclei formed by ZnO NPs inside tumor cells augment mitotic and interphase apoptosis, leading to increased cell death. ZnO NPs loaded with asparaginase improve the selectivity and stability of the chemotherapy combination of paclitaxel and daunorubicin. Asparaginase is a well-known anticancer enzyme utilized as a chemotherapeutic agent in different anticancer therapies [227]. ZnO NPs have been shown to decrease toxicity and boost effectiveness in conjunction with paclitaxel and cisplatin in managing TNBC cells [228].

Among the new nanocarriers, mesoporous silica nanoparticles (MSNs) are being employed to solve this problem. Meng et al., results revealed that combining DOX and siRNA delivery through MSNs

significantly reduced tumor development *in vivo* and had synergistic effects compared to either drug or siRNA delivery alone [229]. Paredes et al., developed MSNs based multifunctional metallodrug nano-system. Researchers found that nanocarriers inhibited cell mobility and decreased cell viability in MDA-MB-231 cells in a dose-dependent manner. Abundant targeting, better treatment effectiveness, and increased tumor shrinkage were seen *in vivo* trials with mice harboring TNBC cells [230].

4.4.9. Theranostic nanomedicine

Numerous imaging agents were included in the formulation to track the movement and effectiveness of the active therapeutic ingredient *in vivo*. “Diagnostic and therapeutic agents in one system” is the definition of theranostic nanomedicine [231,232]. First used by Funkhouser in 2002, the word “theranostic” refers to substances with both diagnostic and therapeutic potential [233]. It is hoped that the idea of concurrent medication and contrast agent administration to the site of action would help the individualization of modern medicine. Micelles and liposomes are examples of nano-carriers that bring theranostic closer to clinical use [234]. In treating complicated illnesses like cancer and proliferative tumors, theranostic nanomedicine has been discovered to have a substantial impact since an exact photocopy for each tumor can be generated together with its genetic and proteomic profile [190]. The most effective techniques for theranostic application and distribution of anticancer medicine and an imaging agent are quantum dot (QD) modified nanohybrids (Protein, polysaccharide, lipid, polymer). NPs quantum dots (QDs) are semiconductor crystals with photoluminescence properties and sizes in the 2–10 nm range [235]. Another research demonstrated a considerable cytotoxic impact of Au-SiO₂/QDs micelles theranostic compared to free doxorubicin, which was shown to be associated to the hyperthermic action of Au-SiO₂/QDs micelles theranostic [236]. Increased therapeutic effectiveness and tumor image detection were seen when paclitaxel was encapsulated with CdTe/CdS/ZnS QDs into NLC for theranostic use [237]. Cai et al., developed This enzyme combination, which breaks down into small molecular weight (MW) products (44 kDa) and releases paclitaxel into the tumor microenvironment, making it a potentially useful therapeutic and detection theranostic nanomedicine. The MRI contrast agent Gd-DTPA improved the imaging capabilities of theranostic nanomedicine, leading to a dramatic upsurge in conjugate accumulation in tumors [238]. Choi et al., developed theranostic targeted erythrocyte membrane nanoparticles for cancer management. This work describes, QDs were integrated into the lipid bilayers of EDNs, and the anti-cancer medication doxorubicin was encapsulated into the NPs. TNBC was then targeted by conjugating anti-epidermal growth factor receptor (EGFR) antibody molecules to the surface of EDNs (iEDNs). Results from the biodistribution test and confocal microscopy studies indicated that iEDNs accumulated more heavily in EGFR-positive MDA-MB-231 tumors than non-targeted EDNs in both *vitro* and *in vivo*. The growth of the targeted tumors was considerably slowed by doxorubicin-containing iEDNs (iEDNs-DOX) compared to non-targeted iEDNs. The anti-EGFR iEDNs that resulted were highly biocompatible, circulated in the blood for a prolong period of time, and efficiently targeted TNBC in mice [239]. Tade et al., discussed about the theranostic graphene quantum dots (GQDs) for the management of BC. Author reveled that GQDs used for the Photothermal treatment, hyperthermia therapy, and photodynamic therapy. The author also emphasizes the importance of GQDs as delivery of drugs motifs and as drug carriers [240]. Although there are currently no theranostic authorized by the FDA specifically for TNBC, there is a clear and rising demand for such treatments. Li et al., developed the nanoplatform for the treatment of TNBC with multi model imaging guided chemodynamic/photodynamic/photothermal synergistic therapy. The formulation surface was modified with the hyaluronic acid which helped on the tumor targeting and accumulate the formulation at target site. The proposed nanoplatform has demonstrated its biocompatibility and efficacy in both *in vitro* and *in vivo* settings for

cancer treatment, showcasing its ability to precisely target TNBC through precise NIR fluorescence, magnetic resonance, and photothermal trimodal imaging [241].

4.5. Radiotherapy

A breast cancer advisory committee from the German Society for Radiation Oncology (DEGRO) has been publishing and updating evidence-based practical recommendations for the treatment of breast cancer with radiation for the essential clinical scenarios since 2005 [242]. In order to eradicate breast cancer cells, radiation treatment makes use of high-energy X-rays, protons, or other particles. Radiation therapy is more effective against rapidly dividing cells, such as cancer cells, than it is against slower-dividing cells, such as healthy tissue cells. Invisible and painless X-rays or particles are used in this therapy. The patient will no longer be radioactive following treatment and may safely interact with others, including little ones. Varzandeh et al., evaluated thioglycolic acid-modified bismuth nanosheet for enhanced loading of Mitomycin C that can potentially damage 62.47% of MDA-MB-231 cells (TNBC cell line) via apoptosis pathway [243]. Radiotherapy for the treatment of breast cancer may be divided into the following:

Accelerated partial breast irradiation (APBI): It has been determined that, for carefully chosen patients, women with early-stage breast cancer may benefit from accelerated partial breast irradiation (APBI) rather than whole-breast radiation. During APBI, radiation is particularly aimed at the breast tissue that is near the original tumor location, usually a margin of 1–2 cm of breast tissue around the surgical cavity. The reasoning for this strategy is that metastases tend to form in close proximity to the primary tumor. This method can potentially limit radiation exposure to healthy organs and tissues outside of the targeted area, including the remaining breast, the heart, lungs, rib cage, and chest and shoulder muscles [244,245].

Multicatheter brachytherapy: Brachytherapy is a localized kind of care; it can only be seen in its close surroundings. In patients with early breast cancer who undergo breast-conserving surgery and whole breast radiation therapy, administering a boost to the tumor bed has been shown to decrease the risk of local recurrence. Excellent local control and aesthetic outcomes may be achieved with brachytherapy because of its dose-escalation capability [246,247]. Additionally, for appropriately selected patients with early breast cancer who have undergone breast-conserving surgery, accelerated partial breast irradiation with multicatheter brachytherapy has demonstrated comparable effectiveness to adjuvant whole breast irradiation [248]. It's enticing as a therapeutic option since it shortens the duration of radiation therapy from 3–7 weeks to 2–5 days and significantly lessens the amount of radiation exposed to the breasts, heart, skin, and lungs [249]. To date, brachytherapy has been shown to be the most effective method of irradiating a tiny area with a high radiation dosage. When it comes to treating breast cancer, brachytherapy is one of the tools in the toolbox.

Intraoperative radiotherapy (IORT): In the early 1960s, researchers at the University of Kyoto in Japan reported using IORT on various intra-abdominal tumors. IORT refers to the administration of radiation to the tumor and its bed during surgical procedures. With IORT, large radiation doses may be directed directly to the cancer bed, sparing the surrounding healthy tissue. As part of a multidisciplinary strategy, IORT is often utilized with other modalities, such as maximum surgical resection, external beam radiation (EBRT), or chemotherapy. The effectiveness of IORT has been explored in a broad range of tumor types, including early TNBC, pancreatic cancer, retroperitoneal sarcoma, locally progressed and recurrent rectal cancer, and a few gynecologic and genitourinary malignancies [250,251]. Delivering IORT has been done in a variety of ways. In contemporary clinical practice, X-rays (kV IORT), electron beams (electron IORT/IOERT), and high-dose-rate brachytherapy (HDR IORT) are some of the frequently used modalities for the administration of IORT [252].

External-beam radiotherapy (EBRT): External beam radiation

therapy (EBRT) is the most commonly employed type of radiation therapy for individuals with BC. Cancer cells are targeted and destroyed in this approach using concentrated energy beams. The radiation beams are precisely directed at the tumor site using a device that rotates around the patient's body. High-energy X-rays, protons, or other particles are utilized in breast cancer radiation therapy to eliminate cancer cells [253] effectively. Zangouri et al., conducted the study for observation of breast cancer (BC) patients undergoing intraoperative radiation treatment (IORT). Patients in this study were selected from April 2014 to March 2020 and same age or elder than 45 years old. 252 patients enrolled in total for the research. The patients' average (SD) age was 56.43 ± 7.79 years. In all, 32.9% of patients had a history of breast cancer in their families. Tumor size was 1.56 ± 0.55 cm on average (SD). Patient follow-up lasted 36.3 ± 18.7 months on average (IQR). The author reported the utilizing IORT in a location with few IORT facilities and our adjusted patient selection criteria [253]. Brund et al., the author focuses on the technical elements of interstitial large-dose rate brachytherapy deployment with a step-by-step methodology. Patients were chosen using inclusion criteria modified from GEC-ESTRO standards, and multidisciplinary tumor boards oversaw the process. Twenty patients were treated between July 2017 and January 2020. An overwhelming majority, specifically 94.7% of the treatment plans, met the required standards for adequate coverage of the target volume, appropriate dose delivery, dosage homogeneity, conformation index, and protection of critical organs at risk. Acute grade 1-2 adverse events occurred in 21% of patients, but no incidents of severity 3-4 occurred [254].

Nosrati et al., reported using $\text{Bi}_2\text{S}_3-\text{Fe}_3\text{O}_4$, a new bimetallic nano radiosensitizer, to increase tumor formation and boost radiation-induced DNA damage with minimal side effects. These recently produced NPs include iron oxide and bismuth sulfide metallic NPs, which suggests that they would have a high radiosensitizing capability by forming reactive oxygen species (ROS) to cause DNA damage under X-ray irradiation. Using bovine serum albumin (BSA) as a coating for $\text{Bi}_2\text{S}_3-\text{Fe}_3\text{O}_4$ bimetallic nanoparticles enhanced their blood circulation time, biocompatibility, colloidal stability, and fine-tuned functionalization. Comprehensive in vitro and in vivo tests have confirmed the biocompatibility and safety of these coated nanoparticles and their ability to induce radiation-induced DNA damage through the activation and generation of ROS. Moreover, the nanoparticles have demonstrated radiosensitizing capability in both *in-vitro* and *in-vivo* experiments. Extremely efficient tumor eradication was seen after administration of $\text{Bi}_2\text{S}_3@\text{BSA}-\text{Fe}_3\text{O}_4-\text{FA}$ in a 4T1 breast cancer mouse model exposed to X-ray radiation, without resulting in death or severe damage in healthy tissues [255]. Torres et al., described the effects of various physical activities on tiredness and identified the most efficient means of alleviating this side effect following adjuvant therapy for breast cancer. Randomized clinical studies assessing the effects of physical activity on tiredness in postmenopausal women with a detection of stage I to IV breast cancer were included. Meta-analysis combined data using the standardized mean difference (SMD). 20 controlled clinical studies with a total of 1793 individuals found that regular exercise significantly reduced weariness [256]. Nafissi et al., studied the IORT's effect on angiogenic factor concentrations in breast cancer patients' blood and surgical wound fluids (SWF). Three hundred sixty women who underwent breast-conserving surgery between 2013 and 2018 were split non-randomly into two groups: those who received IORT and those who did not. EGF, DLL4, and VEGF blood levels were all shown to fluctuate significantly before and after surgery. In addition, ROC analysis demonstrated that TGF- and DLL4 may distinguish between early and late illness. Intriguingly, the IORT group had a lower mortality and recurrence rate [257]. Tutzauer et al., check whether there is a connection between tumor HIF-1 positivity and hypoxia gene expression profiles and the success of radiation in terms of patient outcome. Over the course of 15 years, researchers looked for recurrences, and in 20 years, women who had been detected with initial T1-2N0M0 breast

cancer were tracked to see whether they had died. Results showed that patients with HIF-1-positive and -negative initial tumors reaped the same benefits from radiation. Women with HIF-1-positive initial tumors had an increased chance of both ipsilateral and overall cancer recurrence. Ten of the eleven hypoxia gene profiles studied showed a positive correlation with HIF-1-positivity, and five showed a positive correlation with an elevated rate/risk of recurrence [258].

4.6. Photodynamic therapy

Photodynamic therapy (PDT) is a substitute therapy for cancer that has been revealed to be effective against a range of cancer types with few side effects and has been authorized for use in clinical trials. PDT uses nontoxic photosensitizers (PS) with light to eradicate tumor cells by localizing or removing them within the tumor and in vasculature [259, 260]. Light-activated PSs undergo energy-transfer cascades that generate cytotoxic superoxide anion radicals and reactive singlet oxygen molecules, which may cause cell death [261]. Three interconnected processes are responsible for PDT's antitumor effects: direct cytotoxic effects on tumor cells, indirect damage to the tumor vasculature, and the development of an inflammatory process that might activate systemic immunity. Since neo-vascularization and "leaky capillaries" are tumor features, the nature of the biological effect may be confined to the tumor. An increased photosensitizer concentration in malignant cells may arise from this. A growing body of studies supports PDT's ability to elicit robust immune responses [262]. As a crucial component, the photosensitizer must not be ignored. The ideal PS for use in photodynamic therapy (PDT) for solid tumors would meet some or all of the following criteria: it would be a pure chemical readily available for purchase, it would have low dark toxicity but high photocytotoxicity, it would be highly selective for tumor cells, its wavelength would be long enough to allow for greater light penetration, it would be quickly eliminated from the body, and it would have multiple administration options (oral, intravenous, intertumoral or inhalational) [263,264]. M et al., conducted a phase I/IIa dose escalation trial involving 12 female patients with a recent diagnosis of invasive ductal BC, who were scheduled to undergo mastectomy as their initial treatment. As part of the treatment, the patients received an intravenous administration of the photosensitizer verteporfin at a 0.4 mg/kg dose. Subsequently, the patients were exposed to increasing light doses of 20, 30, 40, and 50 J (with three patients receiving each dosage), delivered through a laser fiber positioned interstitially under ultrasound guidance. Before PDT and again 4 days later, patients had MRI (magnetic resonance imaging) scans. The tissue that was removed underwent a histological analysis. There were no reported side effects with PDT. A strong connection was observed between the MRI and histological findings, suggesting that the PDT effects were present in both cases. Histologically, PDT necrosis differed from spontaneous necrosis in many important ways. Adjacent normal tissue showed signs of apoptosis. No negative effects were seen, and outcomes were not worse than those in the control group, during the course of the median 50-month follow-up. This research lends credence to the idea that PDT might be useful in the treatment of early breast cancer [261]. Kim et al., Here the author introduces a self-luminescent and biodegradable protein-based PDT system based on the protein complex Luc-RGP, which consists of luciferase and a protein capable of generating reactive oxygen species (ROS), was utilized in the study. When breast cells treated with coelenterazine-h, a substrate for luciferase, were exposed to Luc-RGP in the absence of external light irradiation, malignancy in these cells was eradicated. This effect was achieved by combining Luc-RGP with a short lead peptide, which induced the production of bioluminescence-sensitive ROS in the plasma membrane, leading to cell death in the breast cancer cells. Targeted effects were shown with BLiP-PDT even at low light intensities in patient-derived primary breast tumor cells and in *in-vivo* tumor xenograft mice models. These results indicate that BLiP-PDT has immediate application as a potential theranostic strategy against a wide range of malignancies

[265]. Ashkbar et al., reported the nanocomposite (NC) dual photodynamic and photothermal therapy for the treatment of an animal model of BC in the Balb/c mice strain. In photothermal therapy (PTT), hyperthermia is generated using laser light or other heat sources to raise the temperature of cancer cells, ultimately leading to their destruction. On the other hand, in PDT, a photosensitizing reagent is administered to the patient, and it is then activated by laser light of a specific wavelength. This activation produces reactive oxygen species (ROS) that selectively damage and kill cancer cells. PTT and PDT are non-invasive therapeutic approaches used in cancer treatment. The result reveals that tumor volume in the NC + PDT + PTT group was 27% lower than in the baseline condition. It's important to highlight that the therapies didn't cause any noticeable weight loss or side effects in the key organs. Apoptosis was also shown by the IHC data, which showed that the growth of proapoptotic Bax and Caspase3 proteins was considerably greater in the NC + PDT + PTT group against to the control group [261]. HA-ICG-Fe-PDA, which showed photosensitivity and near IR range, has been developed by Li et al. resulting in better photothermal performance in 808 nm laser irradiation. The nanoplatform can actively target CD44-overexpressed TNBC [266,267]. Chen et al., fabricated a MnO₂-coated Prussian blue nanoparticle showing 21.4% reduced cell viability in a combined in-vitro photodynamic/photothermal study. This method achieved tumor inhibition rates of up to 93% against TNBC [268].

4.7. Chemotherapy

Chemotherapy, as defined by Sporn, "involves the administration of pharmacologic or natural agents with the goal of preventing or treating invasive breast cancer by preventing or treating the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells in which such damage has already occurred" [269]. In chemotherapy, medications are often used to kill cancer cells and prevent them from multiplying. Adjuvant chemotherapy is given after surgery, while neoadjuvant chemotherapy is used before surgery to shrink big cancer cells [270]. In cases of early and locally progressed breast cancer, combination therapy is often more beneficial than single therapies. A few of the most frequent treatments for breast cancer are covered here [271]. Carboplatin and cisplatin are platinum-based chemotherapeutic agents commonly used in cancer treatment. These compounds are used alone or in combination with other medications to combat various types of cancer. The mechanism of action of platinum compounds involves forming covalent bonds with DNA, forming platinum-DNA adducts. These adducts cause structural changes and impair DNA stability, thereby interfering with DNA replication and transcription processes in cancer cells. This disruption eventually triggers cell death. The formation of platinum-DNA adducts has been extensively studied both in laboratory settings (in vitro) and within living organisms (in vivo), providing valuable insights into the molecular mechanisms of platinum-based chemotherapy and its impact on cancer cells. The effect of these diverse lesions on DNA replication, mutation induction, and sensitivity to DNA repair techniques have all been measured in preliminary research. Platinum (IV) compounds may cause further DNA damage by being broken down by the cell into platinum (II) compounds [272]. In approximately 20%–35% of cases, patients with metastatic breast cancer experienced an improvement in their condition when treated with carboplatin as a monotherapy [273]. Cancer management with Platinum compounds is often combined with Gemcitabine and Taxanes [274]. Cyclophosphamide: it is used to stop the spread of breast cancer by interfering with the cancer cells' ability to replicate their DNA. Liver intracellular enzymes convert this prodrug into its active metabolites (4-hydroxycyclophosphamide, aldophosphamide, acrolein, and phosphor amide mustard) [275]. Wang et al., prepared a caramelized nanosphere loaded with doxorubicin and Fe₃O₄ that showed better tumor suppression in NIR range and can be used for accurate MRI imaging for TNBC [276]. Zhu et al., prepared PLGA_PEG

nanoparticles loaded with NIR dye and DOX and showed high chemotherapeutic efficiency against primary tumor cells of TNBC. It also produced an antitumor immune response against distant tumors [277].

Taxanes: The most widely used taxanes, paclitaxel and docetaxel, induce mitotic arrest by stabilizing cellular microtubule components. Both monotherapy and combination regimens using these medicines have been successfully used. It has been observed that a weekly maintenance plan of these medicines is well tolerated with little harm in breast cancer [278–280].

Anthracyclines: It is common practice to utilize a combined treatment (i.e., FAC, AC, TAC) that includes anthracyclines like doxorubicin and epirubicin to manage BC. Anthracyclines exert their cytostatic and cytotoxic actions through several suggested mechanisms, such as the generation of free radicals, lipid peroxidation, and direct impacts on cell membranes. These mechanisms contribute to the anticancer properties of anthracycline drugs and their ability to induce cell death in cancer cells. Intercalation, covalent bonding, and base modifications are the best-described methods for interacting with DNA or the DNA-topoisomerase II complex, leading to instabilities in DNA reproduction and transcription and, ultimately, the beginning of DNA repair or programmed cell death [281].

Capecitabine: it is a fluoropyrimidine pro-drug that, when taken orally, is converted into 5-FU by the enzyme thymidine phosphorylase, mimicking the infusion's effects. To complement taxanes, it has been applied to treat patients with metastatic breast cancer who have progressed [282, 283].

Gemcitabine, also known as difluoro deoxy cytidine, is a pyrimidine nucleotide used to treat malignancies of the lung, bladder, breast, and other tissues. Gemcitabine is generally well tolerated when administered through intravenous infusion once weekly [275]. **Vinorelbine** inhibits mitosis by binding to tubulin and stopping the progression of metaphase. Several studies have revealed that this medication has shown encouraging outcomes in treating advanced breast cancer [284]. **Tyrosine kinase inhibitors (TKIs)** include sorafenib, sunitinib, and erlotinib. TKIs inhibit cell growth and proliferation by inhibiting aberrant signal transduction pathways. Many TKIs block more than one signaling route. Anti-EGFR drugs go at a specific tyrosine kinase receptor that has been linked to a wide variety of malignancies [285]. **Vinca alkaloids** it includes vincristine and vinblastine. Drugs mechanisms of action were shown to inhibit cell development by inhibiting mitosis and microtubule polymerization [286].

Topotecan: A topoisomerase inhibitor, topotecan is a camptothecin derivative. DNA damage occurs when topotecan blocks topoisomerase from mending a snipped DNA strand. Apoptosis and cell death occur when topoisomerase is inhibited [287]. Arjum et al., conducted a non-interventional study on 811 females for breast cancer. After the 3–6-month follow-up, the adverse drug events were observed. The adverse occurrences were analyzed for factors such as severity, preventability, and causation, all of which may have been influenced by the use of adjuvant chemotherapy. The results conclude that six cycles of FAC (5-fluorouracil, Adriamycin/doxorubicin, cyclophosphamide) were given to the majority of patients, with positive results. Hair loss, nausea, vomiting, anemia, and neutropenia were identified as non-preventable, definite symptoms suffered by patients after the ADRs were evaluated using various scales. Preventing mild to severe diarrhea or constipation is quite unlikely. Fever and chills are potential side effects, whereas mucositis and mouth ulcers are somewhat likely side effects [288]. kashiwagi et al., conducted a study in 190 breast cancer patients was there about 138 (73%) of 190 TNBC patients did not receive adjuvant chemotherapy; of them, 60 had an anthracyclin-based treatment, and 78 had a 5-fluorouracil-based treatment. The results showed that adjunct therapy improved survival for patients with TNBC, particularly those at Stage II ($P = 0.0043$), against surgery alone. However, neither the anthracycline-based nor the 5-fluorouracil-based therapy improved survival rates [289].

4.8. Immunotherapy

In 1891, William Bradley Coley, now recognized as the Father of

Immunotherapy, injected a variety of *Streptococcus pyogenes* and *Serratia marcescens* bacteria, both live and inactivated, into cancer patients' tumors. The five mainstays of cancer care are surgery, chemotherapy, radiation therapy, and targeted therapy. Immunotherapy is the newest addition to this list [290]. In contrast to healthy people, whose immune systems can quickly eliminate the altered cancer cells, cancer patients often have impaired immune functions that fail to identify and destroy tumor cells [291]. Most tumor cells, however, use a wide variety of strategies to avoid being recognized by immune cells. While immunotherapy effectively eliminates small residual lesions and drug-resistant tumor cells, it is insufficient to eradicate most tumor cells independently. To the maximum degree, it can avoid the drawbacks of many other treatments. In recent years, good outcomes have been seen in the clinical use of cell immunotherapy, a novel method with a targeted killing impact. This therapy is classified in the following:

Immune checkpoint inhibitors (ICIs): ICIs are surface-expressed molecules that suppress cell activation, namely T-cell activation. Its primary function is analogous to an auto-braking cell's mechanism in that it allows the immune system to "brake" within normal parameters after activation, preventing excessive activation [292]. Suppression of immune function due to either an excess of expression or an excess of action of immune checkpoint molecules results in poor immunity and increased vulnerability to tumors and other illnesses. Another way to put it is that abnormalities in the immune system may be attributed to checkpoint molecules inability to perform their immunosuppressive role [293,294].

CTLA-4: The negative regulatory role of CTLA-4 in T cell-mediated immunity is well established. CTLA-4 and CD28 have opposite effects on T cells when they attach to their respective receptors on antigen-presenting cells (CD80 and CD86). CTLA-4 and its ligand mediate T cell response inhibition, whereas T cell response activation is mediated by CD28 and its ligand. CTLA-4 has a stronger attraction for CD80/CD86 than it does for CD28. CTLA-4 overexpression in cancer patients is thought to play a key role in mediating immune escape. Researchers have revealed that TNBC tumor cells express CTLA-4 in a variety of cellular locations [295]. Expression of its primary ligand, CD80/CD86, is seen in TNBC cell lines and malignancies. It follows that the anti-CTLA-4 monoclonal antibody Ipilimumab approved as a checkpoint inhibitor for managing malignancy, may effectively block CTLA-4 and hence greatly stimulate the molecular cascade, potentially enhancing the immune response to tumor cells [295]. Checkpoint inhibitors may be directed towards CTLA-4 expressed on the surface of tumor cells while treating patients with TNBC, making it a potential biomarker for immunotherapy.

PD-1 and PD-L1: The anti-programmed death-1 (PD-1) antibody is one of the most studied and widely used immunotherapies. Various immune cells, including T cells, B cells, and myeloid cells, express PD-1 when activated. The human immune response is negatively regulated by the binding of PD-1 and PD-L1, which mediates the co-inhibitory signal of T cell activation and inhibits T cell death [296–298]. Immune tolerance is maintained in a healthy immune system by PD-1. Immune escape is a mechanism through which tumor cells might evade immune monitoring. Currently, immunosuppressive checkpoint immunotherapy and targeted treatment based on immunosuppressive receptors are the most exciting areas in oncology. Furthermore, it is shown that PD-L1 inhibits anti-tumor immunity by blocking the activation signal sent out by T cells via binding to the PD-1 receptor on active T cells [299,300]. Zhang et al., developed the pH-responsive nano micelles loaded with paclitaxel, CXCR4 antagonist AMD3100, and PD-1/PD-L1 inhibitor. The results revealed that formulation showed cytotoxicity against MDA-MB-231 cells, and IC_{50} was 105 μ g/mL. A nanomedicine formulation comprising PTX, AMD3100, and BMS-1 emerges as a potent strategy, efficiently curbing tumor progression and diminishing liver/lung metastasis. This approach accomplishes reprogramming the tumor stroma and immunosuppressive microenvironment, effectively triggering antitumor immune responses by inhibiting the CXCL12/CXCR4 axis and the induction

of immunogenic cell death [301].

4.9. Herbal therapy

Humans have been investigating new plant species for thousands of years in search of those with medicinal properties. As a result, they have identified several bioactive chemicals in plants that have considerable therapeutic potential. Studies have revealed that various plant compounds, with flavonoids, carotenes, alkaloids, and phenolics, have therapeutic benefits and anticancer potential [302]. Breast cancer is one of the most frequent types of cancer, which is a hereditary illness characterized by the uncontrolled multiplication of abnormal cells inside the body and their migration to other regions of the body. Chemotherapy, which employs cytotoxic chemicals to destroy cancer cells, is the mainstay of cancer treatment. While effective against cancer cells, these chemicals or medications also adversely affect healthy cells. To combat these issues, researchers devote a lot of time and energy to discovering herbal treatments specifically targeting cancer cells. In addition, breast cancer is unique among cancers in that its genetic alterations disrupt several different pathways [303,304]. Cancer is treated using chemotherapeutic drugs derived from plants, most often from their fruits, leaves, flowers, lichens, and fungus. Herbs are defined in botany as fruiting and seed-bearing plants with soft, nonwoody stems [305,306]. These plants and herbs have been crucial in helping to keep people healthy. People are increasingly interested in herbal treatments rather than synthetic medications because of the natural active component in herbals that may aid human health. Many herbal substances with specific cytotoxicity have been reported in recent years, suggesting their potential application as chemotherapeutics. Different herbal preparations were also found to prevent or alleviate treatment-related adverse events, improve quality of life, and lower stress levels [307]. Some commonly used herbs worldwide in treating breast cancer are Echinacea, garlic, turmeric, burdock, carotenoids, green tea, ginseng, black cohosh, flax seed, and vitamin D [308]. Mi et al., developed the formula for treating TNBC using baipuhuang keli by hindering DNA damage repair via MAPK/ERK pathway. The results highlight that BPH exhibited greater susceptibility towards TNBC cells than mammary epithelial cells. BPH demonstrated a substantial dose-dependent reduction in the growth of TNBC cells. Moreover, BPH induced DNA damage in TNBC cells in a manner contingent on both time and concentration. Intriguingly, BPH restrained the DNA damage response (DDR) in TNBC cells. It was observed that introducing EGF alongside BPH activated the MAPK/ERK pathway, potentially enabling DNA damage repair. This anti-proliferative impact of BPH on TNBC was further affirmed through its efficacy in the 4T1 orthotopic tumor model and the MDA-MB-231 subcutaneous tumor model [309].

Echinacea: The genus Echinacea is classified as a member of the Asteraceae family. Primarily cultivated in the Great Plains and eastern regions of North America, this aromatic plant is also grown in Europe. Echinacea purpurea, Echinacea angustifolia, and Echinacea pallida are the three most prevalent species of Echinacea utilized in herbal medicines. Nevertheless, E. purpurea is widely used in academic research and clinical practice. The number of natural killer cells in mice exposed to E. purpurea was shown to increase. One day, E. purpurea may be used as a cancer-fighting medicine [310]. Abraham et al., Studies have demonstrated that when treated with echinacea angustifolia extract combined with paclitaxel, human breast cancer cell lines MDA-MB-231 and MCF-7 exhibit apoptosis and cell cycle arrest responses [311].

Garlic: Allium sativum, or garlic, has been used medicinally for hundreds of years. Alliin, alliinase, and allicin are only a few of the hundreds of therapeutically beneficial secondary metabolites involved. Garlic oil contains allicin, an amino acid generated when garlic rhizomes are crushed. Allicin, a sulfur-containing molecule, was one of the first of its kind and is essential for both the smell and the medicinal benefits of garlic. The high levels of organic sulfides and polysulfides in garlic are accountable for its anti-cancer action. Stimulating anti-tumor activity by

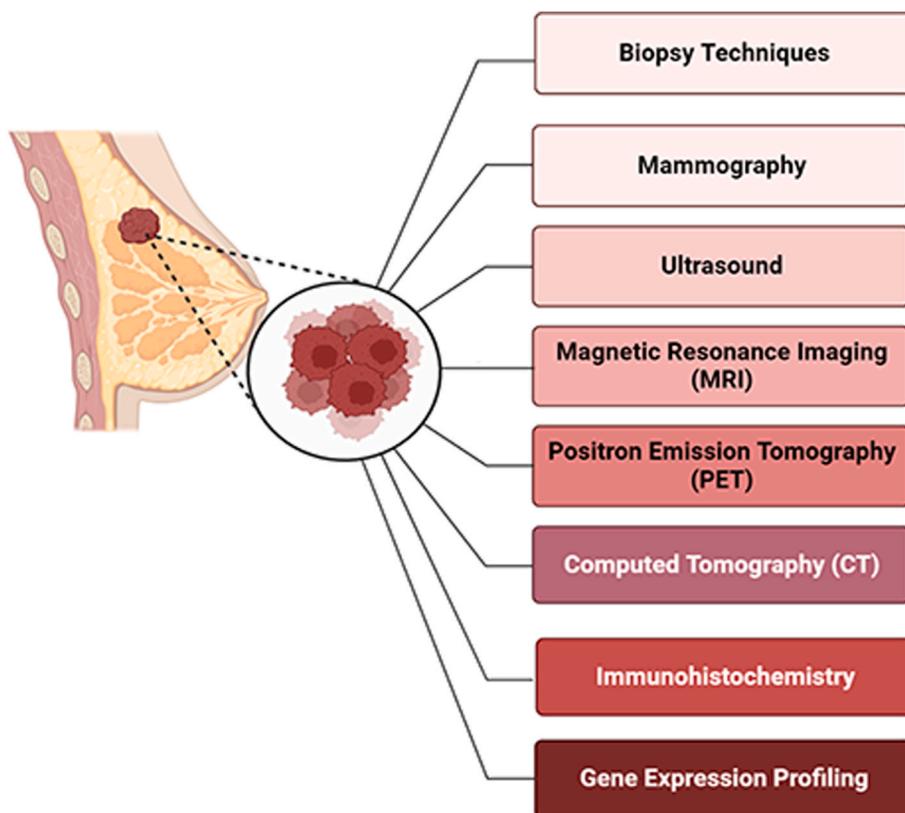


Fig. 6. Diagnosis techniques for the TNBC.

lymphocytes and macrophages kills malignant cells and disrupts the metabolism of tumor cells [312]. Tsubura et al., discussed about the use of garlic and its derivative for the treatment of TNBC. The mechanisms of action for *echinacea angustifolia* in the context of TNBC treatment include stimulating carcinogen-detoxifying metabolizing enzymes, preventing DNA adduct formation, suppressing ROS production, regulating cell-cycle arrest, and inducing apoptosis. These combined actions contribute to its potential anticancer effects and make it a subject of interest in cancer research [313].

Turmeric: Turmeric, or *Curcuma longa*, is the plant's scientific name. Turmeric is responsible for the deep yellow hue it imparts to dishes. Turmeric's rhizome and rootstock are where you'll get the active component, curcumin. The phenolic compounds in curcumin are responsible for its anticancer properties. The use of turmeric slows cancers of the lung, breast, skin, and stomach. Cancer growth inhibition by curcumin has been shown during the disease's induction, promotion, and dissemination stages. Turmeric reduces nitric oxide (NO) production, which boosts the body's endogenous antioxidant defenses [314].

Carotenoids: Besides being a leafy green herb, rose hips also contain an active component called carotenoids. Saffron, annatto, and paprika are just a few of the fragrant plants used to make different dye colors. In many animal models, fruit and vegetable consumption is associated with slower tumor growth. A diet rich in carotenoids may help prevent cancer [315].

Vitamin D: Sunlight on the skin results in the body producing vitamin D. In the summer, just exposing your arms, hands, and face to the sun may generate a substantial quantity of vitamin D. To get the same amount of vitamin D2 as if you took 20,000 IU orally, all you have to do is stand in the sun until your skin becomes pink at the beach. Vitamins are essential for proper bodily function, and we need at least 1000 international units (IU) daily. The only way to keep your vitamin D levels stable while not outside is to take vitamin D supplements orally. The safe daily maximum is 4000 IU, which may be taken in one dose and

has additional advantages. This form of vitamin D is the active form, and it has anti-cancer properties [316]. Wilhelm et al., reported the synergistic effect of paclitaxel with vitamin D on the DU4475 cells of TNBC [317].

4.10. Nanorobots controlled by artificial intelligence for use in cancer treatment: a possible future

The term "artificial intelligence" (AI) refers to the subfield of computer science that focuses on developing automated systems capable of performing tasks that typically require human intelligence. These AI systems are trained to learn from data and adapt their behavior, enabling them to perform problem-solving, pattern recognition, language understanding, and decision-making tasks. AI has seen significant advancements in recent years and is applied in various domains, including natural language processing, image recognition, robotics, and autonomous vehicles [318]. To improve model performance and uncover previously unseen patterns in data, computers use a subfield of artificial intelligence known as machine learning (ML) [319]. It has been predicted for some time that AI will be used to revolutionize the medical industry by simplifying previously intractable problems. Oncology significantly depends on scoring systems derived from evidence-based therapy for cancer risk analysis, illness diagnostics, prognostic staging, therapy, and surveillance monitoring. Gene expression tests and next-generation sequencing of somatic and germline genomes are two examples of the types of sophisticated testing that have increased the effectiveness of systems that often began from very straightforward light microscopy findings. The use of deep sequencing to identify all types of cancer in a person's blood is a promising new method for screening for the disease. Since all cells in the body have access to the circulatory system in some way, whether it is directly or indirectly, analysing whole blood is appealing [320]. By learning patterns from the whole transcriptome, ML/DL algorithms can circumvent the restrictions of

traditional computational approaches. For instance, one ML method has been shown to accurately identify a cancerous state and discriminate it from normal cells by using whole-transcriptome RNA sequencing data and incorporating multiple tumor profiles; this method also performed well for rare cancer types and showed utility in predicting the tumor site of origin [210]. Similarly, transcriptome data has been used in conjunction with neural networks to identify molecular subtypes of different malignancies [321].

Drug uptake assessment by image analysis is a lengthy process. Artificial intelligence is now being applied in identifying and diagnosing cancer using radiographic imaging. The use of computer-assisted detection in TNBC imaging has a long history but has not shown any therapeutic relevance [322]. This is why research into AI-based cancer diagnosis has focused heavily on breast cancer imaging. For instance, AI-based models are now often employed in the clinic for breast imaging. At present, the Food and Drug Administration in the United States has authorized at least five algorithms for detecting and diagnosing breast cancer in imaging studies [323]. The application of AI for tumor identification and diagnosis is not limited to only breast cancer. Multi-parametric magnetic resonance imaging (MRI) has been shown to improve the identification of clinically significant malignancies in several diseases, including prostate cancer [324].

5. Diagnostic techniques for breast cancer

The clinical characteristics of TNBC include rapid disease advancement, metastasis to other parts of the body, an earlier onset age, and a high rate of mortality. Unfortunately, there are currently no specific medications designed to treat TNBC. However, administering neoadjuvant chemotherapy before surgery has been found to be effective in considerably prolonging the survival period of patients. Therefore, achieving an early and precise diagnosis is crucial for effectively managing TNBC. Different techniques for diagnosis of TNBC are shown in Fig. 6.

5.1. Imaging technique

A typical two-step procedure involving imaging and immunohistochemistry (IHC) is used to diagnose TNBC [355]. The imaging technique includes.

5.2. Mammography

Mammograms are frequently used as the first imaging method to screen for breast cancer. They utilize low levels of X-rays to produce precise images of breast tissue, aiding in detecting any potentially concerning regions. Detecting TNBC through mammograms involves identifying calcifications (white spots), growths, or masses. Usually, malignancy is indicated by abnormal spiculated groups and varied micro-calcifications, which are not typically observed in the case of TNBC [356,357]. The usual representation of TNBC on mammography is as a mass without any microcalcifications (white spot). Around 18% of TNBCs may not be detectable during the initial mammography even though they are bigger in size than other forms of breast cancer [357–359]. After analyzing TNBC mammograms in mediolateral oblique and craniocaudal view, most cases are found to have a mass (62.4%). Among these masses, those with micro-lobulated margins were the most frequent (39.6%), followed by unidentified (32.0%) and circumscribed (20.8%) margins. However, masses with spiculated margins were rare (4.7%) [360]. Moreover, 49% of patients suffering from TNBC calcifications are absent. TNBC may be characterized as focal asymmetry in 9–22% of cases or as calcifications along with a mass in 15% of cases. In comparison to HER2-positive (67%) and ER-positive cancers (61%), isolated calcifications are less common in TNBC [361]. Study found that presence of calcification in TNBC varies on the basis of the age of the patients. In women aging 40 years and younger, up to 88% of cancers

had calcifications accompanying invasive cancer, whereas in women of age 70 years and older, only 22% of cancers had calcifications [357,362,363]. The absence of mammographic calcification signifies a lower occurrence of associated ductal carcinoma in situ in TNBC. Thus, TNBC can quickly progress into an invasive cancer without a significant in situ component or precancerous stage. The specific characteristic of circumscribed mass without microcalcification of TNBC signifies it as an aggressive and fast-growing tumor with a chance of being associated with ductal in-situ carcinoma [357].

The primary challenge of detecting TNBC by mammography lies in the chance of getting both false-negative and false-positive results, which can impact the effectiveness of the patient's treatment [364]. Using mammography to detect early TNBC in young females, who typically have a worse outlook, may not be the most suitable approach [357]. Furthermore, individuals having high-risk of breast cancer, such as those carrying the BRCA gene or with a family history of breast cancer, the radiation from mammograms may contribute to the development of breast cancer [365]. Lastly, the accuracy of mammography can vary depending on the operator, potentially affecting the imaging results [356,366]. Hence, mammography alone is often not the most effective method for screening TNBC. Therefore, further exploration of the effectiveness of additional imaging methods such as sonography, magnetic resonance imaging, and functional imaging is recommended to improve the accuracy of diagnosis [357].

5.3. Ultrasound

Ultrasound, which utilizes sound waves, generates live images of breast tissue. Its primary role is to differentiate between solid masses and fluid-filled cysts. It is frequently utilized to examine the detected findings of a mammogram further. Ultrasound can detect potentially concerning regions in the breast, such as abnormal growths or clusters of cells that might suggest the existence of TNBC [367]. It can also deliver detailed dimensions, form, and location of the tumor for assessing the stage and extent of TNBC. With the assistance of ultrasound, directing the needle during biopsy can enable exact tissue collection from the suspicious region for further verification. Furthermore, tracking the treatment efficacy by evaluating tumor dimension and blood circulation can also be monitored via ultrasound. Ultrasound diagnosis is used when a mammogram does not detect a lump or swelling that can still be felt. It is the primary method to differentiate between breast cysts (fluid-filled sacs) and tumors [367–370].

Studies have found that in ultrasound, TNBC commonly presents as mass lesions characterized by oval or round shapes (48.9%, 17.8%; respectively). Additionally, it is more likely to exhibit well-defined boundaries (82.2%), and less likely to exhibit posterior attenuation (8.9 indicating a lack of stromal reaction, which suggests an aggressive and rapidly growing nature of TNBC %). Additionally, compared with non-TNBC, TNBC was a low likelihood to have calcification (35.6%) [371]. Studies showed that in ultrasound, TNBC often exhibits invasive tumor sizes larger than 2 cm (56.1% out of 41 cases), more frequently compared to non-TNBC cases. However, a higher incidence of axillary lymph node positivity in TNBC (56.1%) can be observed compared to ER-positive cancer (31.3%) and HER2-positive cancer (30.3%) [368,371,372]. Specific ultrasound features commonly observed in TNBC include a well-defined boundary in approximately 21%–27% of lesions and posterior acoustic enhancement in about 24%–41% of cases [358,360,369,373]. Well-defined margins are commonly seen in benign breast malignant tumors, cysts, or abscesses but posterior acoustic expansion (53.3%) can also indicate the presence of internal fluid, such as tumor necrosis, which is frequently observed in TNBC upon pathological evaluation [361,374,375]. Elevated occurrence of micro-lobulated margin in TNBC (48.8%) compared to ER+ and HER2+ cancers can be a significant factor for avoiding false-negative cases of TNBC [371]. A new approach to TNBC diagnosis is therapy and diagnosis via nanocarriers called as theranostic. Xiao et al. found that

melanin carbonaceous dots (MCDs) can be a potential diagnostic option in photoacoustic imaging as well as ultraviolet imaging for TNBC as TNBC cell line 4T1 uptakes the MCDs in a time and concentration-dependent way [376]. Similarly, Xie et al. found that semiconducting polymer nanoparticles showed amplified photoacoustic properties in *in vivo* breast cancer imaging in mice [377].

Ultrasound examinations offer several advantages, including cost-effectiveness and the absence of radiation exposure, making them widely utilized in clinical diagnosis [378,379]. Analyzing the texture of ultrasound images can detect subtle pixel changes. This texture analysis provides an additional objective diagnostic tool, enhancing the efficiency of differential diagnosis of TNBC. Additionally, ultrasound improves the accuracy of mammography by increasing specificity, thus reducing false negatives in dense breasts and minimizing unnecessary biopsy recommendations [380]. Overall, ultrasound demonstrates a high sensitivity for detecting TNBC, ranging from 92% to 100% across various studies. However, there are some drawbacks to ultrasound examinations. They heavily rely on the operator's expertise and lack reproducibility, making interpretations subjective. Furthermore, the lack of a standardized procedure for lesion classification and recommendations creates confusion among physicians, radiologists, and patients [381].

5.4. Magnetic resonance imaging (MRI)

Breast MRI employs a powerful magnet and radio waves to produce highly detailed images of the breast. It is a highly sensitive imaging technique that can effectively assess the presence and extent of breast cancer. Additionally, it can detect additional tumors that might not be detectable through other imaging methods. It has been extensively reported that magnetic resonance imaging (MRI) is used to screen people who are at a high risk of getting breast cancer [356,361,382]. A UK multi-center study found that MRI has an overall sensitivity of 77% and specificity of 81%, whereas mammography has a sensitivity of 40% and specificity of 93%. This indicates a substantial advancement in MRI detection [383].

Breast MRI is typically recommended when a suspicious breast abnormality is detected through a mammogram, ultrasound, or physical examination, further information about the area may be obtained by recommending an MRI. MRI can be used to assess a tumor's features, size, and extent. Additionally, it may reveal whether cancer has spread to neighboring lymph nodes or other breast tissues. This information plays a crucial role in staging the cancer and selecting the most suitable treatment approach. Women at a higher risk of developing breast cancer, such as those with a family history of the disease or BRCA genetic mutations, may undergo regular breast MRI screenings as part of their surveillance plan. As it detects the initial stages of breast cancer more accurately than breast ultrasound and mammography, it is also utilized to evaluate the severity of the carcinoma.

The most common enhancement pattern that is observed in TNBC via MRI, which is highly indicative of malignancy, was rim enhancement. This pattern was found in 76% of the cases [373]. At least 90% of all TNBCs have invasive ductal tumors with high mitotic nature, central necrotic sections, and pushing boundaries. These aggressive biological characteristics are reflected in the MRI appearances of the tumors. Studies found that 21% of the tumors exhibited multifocality, and the mean tumor size was 4.1 ± 2.7 cm [361,384,385]. Through dynamic contrast-enhanced MRI (DCE-MRI) parameters that are commonly found in other breast cancer subtypes, such as the distribution of fibroglandular tissue (FGT) and background parenchymal enhancement (BPE), mass margin, non-mass enrichment distribution, and enhancement pattern, lymph node status, and several types of kinetic curves, are still maintained in the MRI [386,387]. Furthermore, it was observed that prominent skin enhancement raised concerns of dermal lymph drainage in 34% of lesions having less than 5 cm diameter. Additionally, 79% of the patients were diagnosed with stage T2 or higher at the time of initial

examination in the case of TNBC compared to non-TNBC (62%) [388]. It is also reported that in TNBC, 93% of patients showed substantial homogeneous and heterogeneous enhancement (23%, 31%, respectively), 41% exhibited rim enhancement, and 78% demonstrated a measurable choline peak through MRI [387,389]. Most significant features that can be seen in MRI are smooth tumor margin with rim expansion, persistent enhancement pattern, and elevated intra-tumoral signal intensity on T2-weighted imaging. In contrast, uneven mass shape and non-circumscribed margins are more commonly linked with non-TNBC [390,391]. Regarding functional imaging, the mean apparent diffusion coefficient (ADC) values are considerably higher for TNBC than non-TNBC. Another study reported vascular characteristics of TNBC where TNBC was compared to ER-positive/PR-positive/HER2-negative cancers using contrast-enhanced MRI. The results showed significantly higher outflow rate constant (kep) values for TNBC (0.70 vs 0.56), lower leakage space values (0.33 vs 0.39), and shorter mean transit time (44.27 vs 47.69) in TNBC [392]. Another study revealed that rim enhancement can be considered the most effective MRI feature for detecting TNBC and this type of enhancement is related to higher stage tumors. A significant association has been found between increased signal intensity on non-boosted fat-suppressed T2-weighted images that corresponded morphologically and pathologically to intra-tumoural necrosis [389]. To improve T1-weighted MRI for TNBC, Zhang et al. created a gold nanocomposite with a metal-organic framework (AuN-S@MOF-ZD2) that is capable of interacting with ZD2 peptide, which yielded 40.5% more efficiency and consistent photothermal conversion capability for MRI [393]. Gold nanoparticles (AuNPs) have been extensively used in diagnosing breast cancer as tumors collect AuNPs, thus being detected in MRI [394]. Another approach includes low molecular weight amphiphilic copolymer that yields a fluorous particle that can detect TNBC using F¹⁹ MRI. Systemic administration of the fluorinated tracer resulted in significant uptake in TNBC, with minimal accumulation in off-target tissues [395].

Additionally, Schmadeka et al. suggested that MRI is the most sensitive imaging modality for detecting TNBC, with a sensitivity of 99–100% [396]. However, it should be noted that breast MRI cannot classify the specific types of breast cancer and it can only provide evidence of the presence of tumors in the breast. Compared with mammographic, ultrasound, and MRI findings in patients on TNBC, it was found that TNBC were visualized among 91% of patients using mammography and 93% using ultrasound. However, MRI can detect all tumors. Thus, it is generally not used as the sole diagnostic tool for breast cancer. It is often used with other imaging techniques like mammography and ultrasound and additional diagnostic tests such as biopsies to form a comprehensive diagnosis before definitive surgery [388]. Although Wu et al. discovered that DCE-MRI characteristics of breast cancer, along with background parenchymal enhancement (BPE), have the potential to differentiate among molecular subtypes of TNBC, these need further investigation [397].

5.5. Positron emission tomography (PET) scan

Positron Emission Tomography Scan (PET scan) is an imaging technique that utilizes a radioactive substance to assess the functionality of organs and tissues. It is recognized for its ability to detect certain diseases even before different imaging methods can identify them. In this process, the radioactive substance, known as a tracer, consists of molecules (isotopes) that carry radioactive atoms tightly linked together. These isotopes bind with some specific biomolecules (such as sugar or protein) present in the body, generating positrons that interact with surrounding electrons and produce photons. The PET scanner detects the electrical signals emitted by these photons and further utilizes the acquired data to create an image of the investigated organ, tissue, or cell. These scans can be used to find any cases of cancer that have spread outside of the breast, such as in distant organs or lymph nodes [356]. With a sensitivity of up to 97% and a specificity of 100%, PET can more

precisely identify axillary lymphatic node metastases in primary TNBC than in ER+ and HER2+ tumors [361]. Nanoparticles used for diagnosis of TNBC, like zirconium labelled PEGylated gold nanocord coated with mesoporous silica nanoshell, showed 4.7 fold stronger imaging of 4T1 breast cancer cell line in PET scan on mice [398].

Immuno-PET imaging, a similar technique, combines the PET system and monoclonal antibodies (mAbs) to improve the precision of tumor diagnosis and aid in selecting the most effective targeted mAb-based therapy [399]. The primary purpose of the antibody in this approach is to recognize specific cancer markers or components on the cell surface or extracellular matrix (ECM), which are subsequently identified by the PET system [400]. Detection of the ATL-836 fragment antigen-binding (Fab) chimeric mAb, which targets the tissue factor found in humans (TF), has supported this strategy. Future developments in the diagnosis and therapy of TNBC have a lot of potential, thanks to identifying the ATL-836 antibody. To prevent apoptosis (cell death) and promote cell migration, platelet tissue factor/factor III (TF), an essential component of cancer cell signaling, is required by TNBC cells. TF is present on TNBC cells [401–403]. In 2017, a new diagnostic imaging antibody was developed and tested in a xenograft animal model for TNBC. This antibody specifically targets a protein known as glycoprotein non-metastatic B (GPNMB) or osteoactivin. The discovery of this technique is vital because GPNMB expression is found to be significantly higher in TNBC patients, particularly in tumor progression recurrence. Furthermore, when the antibody was attached to a toxin, it effectively inhibited the proliferation of TNBC cells expressing GPNMB [356,404,405]. Hence, immuno-PET imaging helps not only with the early identification of TNBC but also aids in identifying a suitable therapeutic approach for each patient. This is because immuno-PET imaging allows us to visualize the expression of therapeutic targets [356]. Though 2-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET) shows potential for detecting distant metastases and monitoring the response to chemotherapy in breast cancer patients, it is not recommended as the main diagnostic procedure for breast cancer. Preliminary data suggests that PET may be more sensitive for the TNBC subtype, as it exhibits higher 18F-FDG uptake than ER+/PR+/HER2-tumors. This is likely due to increased glycolysis and high proliferation rates [361,406].

5.6. Computed tomography (CT) scan

CT scans use multiple x-ray images to generate cross-sectional images of the body. CT scans are useful for evaluating the spread and severity of tnbc. They provide valuable details about the tumor's size and location, involvement of nearby lymph nodes, and potential spread to other organs.

TNBC patients often exhibit varied and inadequate responses to identical treatment plans due to the tumor's heterogeneity. Image signatures can quantitatively extract tumor images, providing a more comprehensive and subjective approach. Moreover, this method is non-invasive and offers quantitative descriptions of tumor heterogeneity. MRI has a higher resolution in soft tissue than CT, but it is more expensive and takes longer to examine. Diagnosis of axillary lymph node metastases in TNBC, similar to primary TNBC, is more accurately done using PET/CT scans (with 100% accuracy and up to 97% sensitivity) compared to ER+ and HER2+ tumors [407]. In accord to CT scan, researchers found that PEG-attached gold nanoparticles can specifically attach to HER2, leading to improved CT imaging in contrast with iopamidol (commonly clinically used iodine-based contrast agent) in mice [408]. Mesoporous silica NPs, and surface-modified mesoporous silica NPs with platinum NPs have also been found to be significant in creating optical contrast in CT in mouse models by Chu et al. [409]. Studies found that radiomic signatures based on preoperative CT can differentiate between patients with TNBC and non-triple-negative breast cancer (NTNBC) [407]. This signature provides additional value compared to conventional chest contrast-enhanced CT, assisting in planning clinical treatment strategies for these patients. Additionally,

hybrid imaging techniques such as PET-CT have become more widespread due to improved accessibility to radiopharmaceutical production facilities and scanner availability. In TNBC bone metastases, the clearance of 18F-sodium fluoride (18F-NAF) is significantly higher than in healthy bone, making detecting both osteolytic and osteosclerotic metastases possible. Compared to 18F-NAF PET alone, 18F-NAF PET-CT displays better diagnostic performance without the CT component [410]. However, it is crucial to realize that TNBC cannot be accurately diagnosed with CT scans alone. A biopsy, which involves taking a sample of the tumor for microscopic analysis, is required to provide a definitive diagnosis. This enables in-depth examination of cancer cells, notably their hormone receptor status and expression of HER2/neu, which are important indicators of the particular subtype of breast cancer [385].

5.7. Biopsy techniques

A tissue sample from the breast is collected and placed through a pathological test to determine the presence of TNBC and comprehend its unique characteristics. A core needle biopsy is the fundamental technique for identifying TNBC. Large hollow needles called core needles are used during this technique to extract microscopic cylindrical samples (cores) of breast tissue. Typically, local anesthetics are used, and imaging methods like ultrasound, CT scan, MRI, or mammography are used as guides. In addition to these other methods, TNBC can be diagnosed via liquid biopsy, surgical biopsy, and fine needle aspiration (FNA). During the fine needle aspiration (FNA) technique, fluid or tumor cells are taken out for additional investigation. It is typically used to facilitate sample collection when fluid or cysts are present [411]. When a larger sample is required or the outcomes of a core needle biopsy are questionable, a surgical biopsy may be performed. This may necessitate either an incisional biopsy, in which only a piece of the tumor is removed for analysis, or an excisional biopsy, in which the entire tumor is removed. It is typically used to facilitate sample collection when fluid or cysts are present. When a larger sample is required or the outcomes of a core needle biopsy are questionable, a surgical biopsy may be performed. This may necessitate either an incisional biopsy, in which only a piece of the tumor is removed for analysis, or an excisional biopsy, in which the entire tumor is removed [356,412,413]. Additionally, studies have looked into the potential predictive and diagnostic value of serum apolipoprotein C-I (ApoC-I) in TNBC [414].

The concentration of tumor ctDNAs in the blood is influenced by the size of the lesion or metastasis. Studies suggested that tumor burden percentage increases with higher ctDNA concentrations. ctDNA analysis has also been utilized to ensure the diagnosis of metastatic relapse. MicroRNAs (miRNAs) are short RNA molecules composed of around 22 nucleotides. They regulate the activity of thousands of genes by attaching to target mRNAs. Some miRNAs act as oncogenes or tumor suppressors, playing a crucial role in cancer development. Tumor suppressor miRNAs, on the other hand, are often anti-proliferative and pro-apoptotic and are downregulated in cancer cells [356]. The study by Thakur et al. found elevated expression of miR-21, miR-220, and miR-221 in TNBC patients [415]. Frères et al., created a new screening tool for breast cancer by using diagnostic test based on eight circulating miRNAs (miR-16, miR-103, miR-107, miR-148a, miR-19b, miR-22, and let-7d, let-7i). This test can identify breast cancer malignancy and detect early breast cancer incidences. It produces consistent results regardless of the patient age or tumor stage [416]. Research has found that exosomes derived from TNBC cells can facilitate cell communication and transfer phenotypic traits to secondary cells. It has been discovered that these TNBC exosomes aid in the development, metastasis, and evasion of the immune system in cancer. Studies have also shown that specific exosome proteins can be used as predictive and diagnostic indicators for breast cancer. For instance, endothelial locus-1 (DEL-1) and fibronectin in circulating exosomes serve as biomarker candidates for detecting early stages of TNBC. CD24 has also been proposed as a potential

circulating biomarker for breast cancer [356,417,418]. Liquid biopsy, which involves the examination of biomarkers in human fluids, provides immediate and accurate results, lowers the expense and length of the diagnosis process, and does not involve the hazards of surgery. This strategy shows promise for the advancement of TNBC diagnosis in the future.

5.8. Immunohistochemistry

IHC, or immunohistochemistry, is a critical component in diagnosing TNBC. IHC aids in the categorization of breast cancer subtypes by detecting the expression of the estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), and progesterone receptor (PR). IHC is performed explicitly in TNBC to use specific antibodies to confirm the lack of ER, PR, and HER2. Given that TNBC often does not react to hormone therapy or targeted medications that target the HER2 receptor, the absence of these receptors is crucial for assessing treatment options [367]. IHC can also be utilized to evaluate additional biomarkers and proteins linked to TNBC, including basal indicators like cytokeratin 5/6 and EGFR, proliferative markers like Ki-67, and particular molecular subtypes like BRCA1 mutation [419]. Regarding the microscopic study of tissue (histology), it was observed that TNBC had a lower occurrence of ductal carcinoma *in situ* compared to HER2+ and ER + cancers. Additional methods like fluorescence *in situ* hybridization (FISH) may be conducted to confirm HER2 negativity in uncertain cases. 82% of TRN cancers were found to be invasive without any evidence of an *in situ* component [420].

Most TNBC are aggressive invasive ductal carcinomas of no specific type, while the remaining cases can be categorized as medullary carcinomas or metaplastic carcinomas. This indicates that TNBC can occur in various histological subtypes of breast cancer, which might have implications for their development, progression, and prognosis. Additionally, TNBC is associated with higher levels of Ki-67 expression, which is a marker of cell proliferation, and these cases generally have a poor prognosis in terms of survival. Immunohistochemistry was utilized to examine the presence of EGFR and ck5/6 in TNBC. In most of these tumors, we identified the expression of at least one of the markers, EGFR and/or ck 5/6, amounting to 74%. Studies found that the individual basal marker, EGFR, was expressed in over half of the triple-negative tumors (64%). However, ck5/6 was described in more than a quarter of TNBC (40%), which is relatively low [421]. To improve the accuracy and effectiveness of IHC testing for ER, HER2, and PR, the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) has provided approximately 126 updated guidelines. These guidelines aim to enhance the reliability and reproducibility of IHC testing while minimizing false-positive and false-negative results. According to the recommendations, IHC testing for ER and PR is classified as positive if only at least 1% of immunoreactive cancer cells are present. Additionally, after the initial IHC confirmation, another confirmatory test of HER2+ should be performed using fluorescent *in situ* hybridization (FISH). This additional step helps prevent potential misdiagnosis that could impact the direction and effectiveness of treatment [422].

5.9. Gene expression profiling

Examining the specific gene expression and proteins can offer a valuable understanding of the molecular traits associated with TNBC. This knowledge holds the potential for the creation of focused therapeutic approaches. To surpass the shortcomings of current techniques like IHC, the gene profile assay presents an efficient alternative. Unlike IHC, which frequently encounters issues such as limited specificity, false positive results, and the absence of precise biomarkers for tumor origin, the gene profile assay proves more reliable. Large-scale investigation of gene expression patterns has been made possible by microarray technologies. Gene expression profiling in TNBC has identified several different subtypes, including luminal androgen receptor, basal-like 1

and basal-like 2 subtypes, and low M2-like macrophages [356]. Genes that control hormone signaling, particularly androgen signaling and synthesis, are more abundant in the luminal androgen receptor (LAR) subtype. Genes including Ki-67, ATR, BRCA, MYC, and NRAS involved in cell division and DNA damage are highly expressed in the basal-like 1 subtype of TNBC. The basal-like 2 sub-type, on the other hand, is characterized by high levels of expression of genes like EGFR, MET, EPHA2, and TP53. The mesenchymal subtype, which is similar to chemo-resistant metaplastic breast cancer, exhibits higher levels of genes linked to cell motility, proliferation, and differentiation, including Wnt, ALK, and TGF. According to a study on African-American women, TNBC and the deletion of the PTEN gene are strongly correlated. Additionally, the discovery of unregulated Wnt-catenin pathway genes in African women as opposed to European women shows that the Wnt-catenin pathway may contribute to the emergence of a more aggressive phenotype of TNBC [423,424].

In the case of TNBC, the genes KRT14 and KRT19 were found to be differentially expressed between basal-like and luminal-like subtypes. Additionally, the expression of SFRP1 was found to be higher in comparison with other breast cancer subtypes. KR15 gene was upregulated in mammary stem cells compared to myoepithelial or luminal cells in TNBC. Studies reported that overexpression of genes like AZGP1, PIGR, SPINK1, RPS11, TACSTD2, and EPCAM can suggest TNBC [425]. Somatic mutations in genes such as TP53, PIK3CA, and PTEN dominate most TNBC. TP53 mutations, in particular, are the most common and can lead to genetic instability and cytogenetic alterations. Loss of TP53 has been associated with enhanced metastasis and worse overall survival. Another essential gene involved in TNBC is BRCA1/2, with around 80% of hereditary TNBC cases carrying mutations in BRCA1. Germ-line mutations in BRCA1 occur in 15% of TNBC cases. Furthermore, alterations in the PIK3CA gene were observed in approximately 10% of TNBC cases. The study also reported six differentially expressed genes (IL32, PTX3, GATA3, TMEM158, ETS1, and MYBL1) that were able to differentiate a subset of TNBC samples from other TNBC subtypes, as well as differentiating TNBC from normal-like, luminal A, luminal B, and HER2 patient samples [423]. Another study conducted in Mexican TNBC patients utilized microarray gene expression profiling and gene set enrichment analysis (GSEA) to identify an overexpression of nine genes (PRKX/PRKY, UGT8, HMGA1, LPIN1, HAPLN3, FAM171A1, BCL141A, FOXC1, and ANKRD11) involved in metabolism [426]. Additionally, one gene (ANX9) was found to be down-regulated. This gene signature provided insights into the metabolic aspects of TNBC. Furthermore, the analysis also revealed that the upregulation of the FOXM1 gene and downregulation of the PPAR α gene were associated with TNBC.

In a study by Komatsu et al. DNA microarray analysis was used to identify 104 genes that are highly overexpressed in TNBC. Several cancer-specific kinases, such as NEK2, PBK, and MELK, and genes involved in mitosis, such as ASPM and CENPK, were identified. These genes could be targeted for upcoming therapeutic research [427]. In China, gene microarray analysis was conducted to characterize TNBC and identified potential biomarkers such as HORMAD1, ELF5, KLK6, GABRP, AGR2, AGR3, ANKRD30A, NME5, and CYP4Z3P. Microarray analysis was used in another study in China to compare the gene expression profiles of several breast cancer subtypes. They discovered COL4A2, BMF, DUSP1, FOXA1, and MLPH as probable candidate TNBC gene targets [423,425,428]. Gene expression profiling, in general, offers molecular characteristics of the illness, revealing possibilities for individualized therapy options. All of these gene expression assays have not yet been approved or suggested for use in TNBC and HER2-negative patients. It should be noted. They have primarily been validated for ER + breast cancers. This highlights the need for further efforts to validate these gene expression assays.

6. Future perspective

Recent advancements in novel drug delivery systems hold immense

Table 2
Patent for TNBC treatment.

Patent	Claim	Patent No.	Patent date	Applicant	References
Compounds for treating TNBC	This patent describes a technique for treating TNBC, whether relapsed or refractory, in patients with the BL1 subtype or BRCA-1 wildtype. It involves administering tinostamustine or salt to the patient appropriate for therapeutic application. Tinostamustine may be used with other medications, such as PARP inhibitors, DNA repair inhibitors, or DDR inhibitors, to treat certain conditions. The patent specifies precise dose levels and delivery techniques. Tinostamustine may be used in conjunction with radiotherapy. For TNBC patients with the specified subtypes and ailments, another embodiment combines tinostamustine with a DDR inhibitor.	US 11,413,276 B2	Aug. 16, 2022	Purdue Pharma LP	[429]
Methods and compositions for TNBC stratification and treatment	The patent claims focus on applying Protein C receptor (PROCR) for TNBC diagnosis and treatment. An H-score of 120 indicates PROCR-high TNBC, which is determined by an immunohistochemical test. For diagnosis and therapy, including cross-competition capacity, specific anti-PROCR antibodies are utilized. The claims include diagnostic tools, pharmacological formulations containing PROCR inhibitors, and strategies for reducing TNBC cell proliferation, metastasis, and EMT using a PROCR inhibitor. In conclusion, the patent suggests potential uses for PROCR in detecting and treating TNBC.	WO 2019/109,331 A1	June 13, 2019	Shanghai Institutes for Biological Sciences, Chinese Academy Of Sciences	[430]
Methods for assessing the treatment response of TNBC patients to neo-adjuvant chemotherapy by analyzing CpG methylation	The technique described in the patent involves examining the methylation status for specific CpG dinucleotides within the PITX2 gene in a breast cancer tissue sample to treat TNBC in a human patient. Depending on the subject's methylation status, the patient is assigned to either an anthracycline-based neoadjuvant TNBC chemotherapy treatment or a non-anthracycline-based TNBC therapeutic treatment. The procedure involves isolating genomic DNA, altering cytosine that hasn't been methylated into uracil, amplifying the PITX2 gene area, and figuring out the methylation level. Different states allow for the provision of breast cancer tissue samples. Based on the PITX2 gene methylation status, this diagnostic method offers customized therapy for TNBC patients.	US 11,230,737 B2	Jan. 25, 2022	Therawis Diagnostics Gmbh, Munich	[431]
Treatment of high Trop-2 expressing triple-negative breast cancer (TNBC) with sacituzumab govitecan (IMMU-132) overcomes homologous recombination repair (HRR) rescue mediated by Rad51	The technique described in the patent involves employing an anti-Trop-2 antibody-drug conjugate (ADC) with SN-38 as a medication to treat TNBC, a malignancy that expresses Trop-2. The medication contains a Rad51 inhibitor. The combo treatment shrinks tumors and could treat metastatic or resistant malignancies. To increase the ADC treatment's efficiency against cancer, several therapeutic methods may be added.	US 10,918,734 B2	Feb. 16, 2021	Immunomedics, Inc. , Morris Plains, NJ (US)	[432]
Markers of Triple-Negative Breast Cancer and Uses Thereof	The method described in the patent enables the identification and treatment of various subtypes of TNBC in human patients. To determine if TNBC IM or TNBC LAR subtypes exist, it is necessary to examine the gene expression in TNBC cells. Then, according to the detected subtype, treatment strategies are given, including immune checkpoint inhibitors for TNBC IM and androgen receptor antagonists with or without PI3K inhibitors for TNBC LAR. The objective is to provide individualized and more efficient treatments for various TNBC subtypes.	US 2020/0224,282 A1	Jul. 16, 2020	Vanderbilt University, Nashville, TN (US)	[433]
Methods and compositions for treating triple negative breast cancer (TNBC)	According to the patent, a technique for estimating TNBC patient life expectancy based	WO 2023/078,900 A1	May 11, 2023	INSERM (National Institute of Health and Medical Research), University of	[434]

(continued on next page)

Table 2 (continued)

Patent	Claim	Patent No.	Patent date	Applicant	References
Method and system for predicting tumor mutation burden (TMB) in triple negative breast cancer (TNBC) based on nuclear scores and histopathological whole slide images (WSIs)	<p>on the expression of SPARC (Secreted Protein Acidic and Rich in Cysteine) in cancer-associated fibroblasts (CAFs) from a biological sample. Shorter survival in CAFs is associated with positive SPARC expression. Anti-SPARC therapy is also covered for treating individuals with a limited prognosis for survival. The patent covers combination therapy for TNBC that uses anti-PD1/PDL1 and anti-SPARC drugs. It also outlines a technique for finding drugs that target SPARC expression in CAFs. A kit with reagents for SPARC mRNA/protein in CAFs and usage guidelines is included in the patent.</p> <p>The technique and system described in the patent involve the use of nuclear scores and histopathological whole slide images (WSIs) to forecast the tumor mutation burden (TMB) in TNBC. The procedure involves screening TNBC WSIs, computing TMB values based on gene mutations, categorising patients into groups with high and low TMB values, preprocessing and segmenting WSIs into patches, extracting nuclear scores, and creating a convolutional neural network (CNN) classification model for TMB prediction. The system consists of a processor and memory where programme codes are stored to carry out the prediction process and produce visual reports of the outcomes.</p>	US 2023/0153,994 A1	May 18, 2023	Wuhan University, Wuhan City (CN)	[435]

promise for the management of TNBC. As research progresses, personalized and targeted therapies are expected to become more widespread, enabling the development of patient-specific drug carriers tailored to individual TNBC characteristics. Combination therapies, integrating multiple therapeutic agents within one platform, will likely play a pivotal role in overcoming drug resistance and achieving synergistic effects, thereby enhancing treatment efficacy. The integration of immunotherapeutic agents with drug delivery systems can bolster the antitumor immune response and improve long-term treatment outcomes. Moreover, the adaptability of nanoparticles and stimuli-responsive drug carriers presents an opportunity to tackle the challenges of tumor heterogeneity, leading to more effective treatment responses and prolonged survival rates. Real-time monitoring of treatment response through theranostic drug delivery platforms will enable clinicians to make timely adjustments based on individual patient responses. Additionally, the utilization of natural drug delivery vehicles like exosomes holds promise for targeted drug delivery with inherent biocompatibility. Therapeutic techniques that consider the individual patient's molecular profile may be made more accessible with omics-guided treatments that include genomic and proteomic data. Integrating novel drug delivery systems with precision medicine strategies will lead the way for a revolutionary era in TNBC management, improving treatment outcomes and enhancing the quality of life for TNBC patients as regulatory hurdles are overcome, and clinical translation is facilitated.

7. Conclusion

In conclusion, TNBC treatment has entered a new era because to innovative medication delivery technologies. These novel strategies are attempts to address the problems associated with TNBC, including as the cancer's aggressiveness and the scarcity of available treatments. Researchers have created targeted, personalized, and stimuli-responsive drug carriers that may increase therapeutic effectiveness while decreasing systemic toxicity using state-of-the-art technology and nanomedicine concepts. Drug carriers that can carry therapeutic

compounds directly to cancer sites have been developed due to the combination of nanotechnology, biomaterials, and cutting-edge imaging methods. Drug accumulation inside TNBC cells may be improved using these drug delivery methods. There is great hope in the battle against TNBC, especially when drug delivery technologies are combined with immunotherapy, gene therapy, and other developing treatment approaches. Targeted delivery of drugs in conjunction with innovative therapies may be the key to unlocking the immune system's full capacity and successfully combating the difficulties presented by cancer heterogeneity. The significance of personalized medication in TNBC treatment will become more critical. More effective and individualized treatments may be possible by developing patient-specific medication delivery systems based on unique cancer features and genetic profiles. However, obstacles remain, such as gaining regulatory authorization, translating research into clinical practice, and scaling up manufacturing. Overcoming these challenges and speeding up the incorporation of innovative drug delivery methods into clinical practice requires ongoing cooperation between researchers, doctors, and industry partners. New medication delivery methods have shown considerable promise in the treatment of TNBC. More beneficial and individually tailored therapy choices that boost health outcomes and standard of living should be expected as research, patents and clinical trials continue as mentioned in [Table 2 and 3](#). In the future, we aim to be able to successfully treat and even eliminate this aggressive type of breast cancer. We believe further developing these technologies will substantially contribute to this fight.

CRediT authorship contribution statement

Ashutosh Gupta: Conceptualization, Writing – original draft. **Kumar Nishchaya:** Writing – original draft. **Moumita Saha:** Writing – original draft. **Gaurisha Alias Resha Ramnath Naik:** Writing – original draft. **Sarika Yadav:** Writing – original draft. **Shreya Srivastava:** Writing – original draft. **Amrita Arup Roy:** Writing – original draft. **Sudheer Moorkoth:** Writing – review & editing. **Srinivas Mutalik:** Writing – review & editing. **Namdev Dhas:** Conceptualization, Software, Supervision, Writing – review & editing.

Table 3

A brief insight of currently active clinical trials against TNBC resistance.

Study title	Nanocarriers/Therapy	Purpose/Outcome	Status	Company	NCT and Reference
A Study to Evaluate Safety/Tolerability of Immunotherapy Combinations in Participants With Triple-Negative Breast Cancer or Gynecologic Malignancies	Pegylated liposomal doxorubicin (PLD) and nanoparticle albumin-bound paclitaxel (NP)	This Phase 1/1b study investigates the safety and efficacy of ertrumadenant (AB928) in combination with different chemotherapeutic agents for advanced metastatic TNBC and ovarian cancer. The study aims to determine the recommended dosing and assess clinical activity in these patient populations.	Phase 1 Study start: 2018-10-15 Study completion: 2021-07-02	Arcus Biosciences, Inc.	NCT03719326
A Phase II Study to Explore the Safety, Tolerability, and Preliminary Antitumor Activity of Sitravatinib Plus Tislelizumab or Combination With Nab-paclitaxel in Patients With Locally Recurrent or Metastatic Triple Negative Breast Cancer (TNBC)	Drugs involved Sitravatinib, Tislelizumab and Nab-paclitaxel	Sitravatinib combined with tislelizumab demonstrated clinically meaningful anti-tumor activity and had a manageable safety profile.	Phase 2 Study start: 2021-04-01 Study completion: 2023-06-30	Fudan University	NCT04734262 [436]
A Study to Evaluate the Efficacy and Safety of Nanosomal Docetaxel Lipid Suspension in Triple Negative Breast Cancer Patients	Nanosomal Liquid Suspension	This randomized, open-label study aims to evaluate the efficacy and safety of Nanosomal Docetaxel Lipid Suspension compared to Taxotere® in TNBC patients, assessing different doses and monitoring disease progression using imaging studies and safety variables. The study involves 657 patients randomized into three arms.	Phase 3 Study start: 2018-07-10 Study completion: 2024-07-31	Jina Pharmaceuticals Inc.	NCT03671044 [437]
Cryoablation and Anti-PD-L1 Immunotherapy for Triple Negative Breast Cancer (TNBC)	Drugs involved Atezolizumab and Nab-paclitaxel Procedure used Cryosurgery	This early phase I trial investigates the safety and feasibility of combining cryoablation, atezolizumab, and nab-paclitaxel in treating locally advanced or metastatic TNBC. Cryoablation freezes the tumor cells, while atezolizumab and nab-paclitaxel aim to enhance the immune response and inhibit tumor growth, potentially improving treatment outcomes.	Early Phase 1 Study start: 2020-01-23 Study completion: 2021-11-17	Mayo Clinic	NCT04249167
A Randomized, Double-Blind, International Multi-Center, Phase III Clinical Study to Evaluate Efficacy and Safety of HLX10	In combination with Chemotherapy (as Neoadjuvant Therapy)	A Tumor assessment is done in this study.	Phase 3 Study start: 2020-04-17 Study completion: 2027-04-09	Shanghai Henlius Biotech	NCT04301739
Nanoparticle Albumin-Bound Paclitaxel Followed by Dose-Intensive Epirubicin in Combination With Cyclophosphamide as Neoadjuvant Chemotherapy in TNBC	Albumin-Bound Paclitaxel nanoparticle	This open-label study aims to evaluate the efficacy and safety of weekly Nanoparticle Albumin-Bound Paclitaxel followed by dose-intensive Epirubicin in combination with Cyclophosphamide as neoadjuvant chemotherapy in TNBC. The primary endpoint is to assess the pathological complete response rate using RECIST 1.1 criteria, with a total of 60 patients expected to be included in the study over a duration of approximately 19 months.	Phase 4 Study start: 2018-11-26 Study completion: 2020-02-01	Fudan University	NCT03799679
Nab-Paclitaxel and Bevacizumab Followed By Bevacizumab and Erlotinib in Metastatic Breast Cancer	Paclitaxel albumin-stabilized nanoparticle formulation along with bevacizumab and erlotinib hydrochloride	This phase II trial aims to assess the effectiveness of paclitaxel albumin-stabilized nanoparticle formulation (Nab-paclitaxel) combined with bevacizumab followed by maintenance treatment with bevacizumab and erlotinib hydrochloride in patients with metastatic breast cancer. The study will evaluate progression-free survival, response rate, overall survival, safety, and exploratory biomarkers, with patients receiving induction therapy followed by maintenance therapy based on their response.	Phase 2 Study start: 2008-04-23 Study completion: 2017-09-28	University of Washington	NCT00733408
A Phase II Study of Abraxane®, Carboplatin and Bevacizumab in “Triple Negative” (Demonstrating No Expression for Estrogen, Progesterone, or Her2 Receptors) Metastatic Breast Cancer	Drugs involved are Abraxane, Bevacizumab and Carboplatin	This study aims to evaluate the efficacy and tolerability of weekly Abraxane® (nanoparticle albumin-bound paclitaxel) in combination with carboplatin and biweekly bevacizumab for the treatment of metastatic breast cancer. The goal is to prolong time to progression without significant toxicity, considering the limitations of anthracycline-based chemotherapy and the potential benefits of targeted biologics.	Phase 2 Study start: 2007-05 Study completion: 2014-03	Duke University	NCT00479674

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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