



Review Article

Novel Strategies for Treating Breast Cancer: A Comprehensive Review

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Citation: Yarahmadi R, Akbarzadeh S, Thompson M, Azizipour E, Shanmugapriya D, et al. (2026) Novel Strategies for Treating Breast Cancer: A Comprehensive Review. J Oncol Res Ther 11: 10355. DOI: 10.29011/2574-710X.10355.

Received Date: 24 August, 2026; **Accepted:** 02 September, 2026; **Published Date:** 05 September, 2026.

Abstract

Breast cancer (BC) is a major health concern worldwide. This review examines risk factors, molecular subtypes, and treatment strategies in this cancer. This manuscript also emphasized cutting edge methods that could enhance outcomes for patients, like immunotherapy and targeting cancer stem cells (CSCs). Along with the promise of immunological checkpoint inhibitors and adaptive cell treatments, the role of immunity in the development and response to BC treatment is discussed. The importance of the tumor microenvironment and the impact of lifestyle factors on the risk of this cancer are also highlighted. Despite tremendous progress, issues such as metastasis and drug resistance still remain. The current inquiry aims to find novel therapeutic targets while developing tailored therapies in order to enhance the prognosis of patients suffering from this type of cancer.

Keywords: Molecular Subtypes; Breast Cancer; Immunotherapy; Tumor Microenvironment.

Introduction

The mammary gland functions as a highly dynamic organ that undergoes multiple stages of transformation. During each estrus cycle during pregnancy, the mammary epithelium proliferates and differentiates in response to both systemic and local cues.

A hierarchical array of progenitors and mammary stem cells (MaSCs), which normally maintain organ homeostasis, promote alveolar formation during pregnancy, and drive mammary ductal elongation and branching, orchestrates these changes [1]. The most frequent malignancy among women diagnosed globally is breast cancer (BC) [2]. Metastasis development is the primary driver of mortality for most cancer patients [3]. The most complicated and lethal event is metastasis. The interface between the tumor and the

surrounding tissue is where tumor cells invade, either by single-cell or, less frequently but more effectively, collective migration [4]. The final and most deadly form of cancer is metastasis, which is the cancer cells' growth in organs other than the one they started in [5]. The most recent statistics from the journal CA Cancer indicate that BC continues to be on the rise and has evolved into one of the most prevalent malignant tumors [6]. This type of cancer is a complicated condition impacted by both genetic and environmental causes [7]. It is important to note that it is the most frequent malignancy among women, accounting for over 316,000 instances of cancer in the US each year. Ductal carcinoma in situ (DCIS), or invasive ductal carcinoma in the milk ducts, is the initial stage of the majority of BCs. Mutational changes over time cause this cancer to develop, which occurs mostly in the ductal epithelium [7]. The World Health Organization (WHO) predicts that, by 2030, there will probably be a considerable rise in the incidence of this kind of cancer as a result of major changes in lifestyles [8]. It is worth noting that this cancer is usually classified using two perspectives: molecular and histopathological. BC in situ and invasive BC are two categories that are divided into different histopathological subtypes. Locally, there are two primary types of BC: lobular and ductal. There are five categories for ductal cancer: comedone, cribriform, micropapillary, papillary, and solid. Lobular classification is based on low pathogenicity. Invasive lobular cancer is classified as tubular ductal, mucinous medullary, infiltrative ductal, and invasive lobular. Molecularly, they are classified into the following groups: Luminal B (HR+[ER+ AND/OR PR+]HER2-/-) - Her2 positive (HR-[ER-PR-]HER2+) - Luminal A (HR+[ER+ AND/OR PR+]HER2-) - TNBC (HR-[ER-PR-]HER2-) - Normal like (HR+[ER+ AND/OR PR+]HER2-) [9-11]. Risk factors for this type of cancer include advanced age, female gender, having a positive family history, early menarche, thick breast tissue, hormone therapy, late menopause, not being pregnant or breastfeeding, and having chest radiation therapy in the past [12]. Cancer is the world's second leading cause of mortality, after heart disease. One-third of women and half of men in the US will have cancer at some stage during their lifespan. Because of early detection and medical care, millions of people with cancer are now surviving longer [13]. With respect to the sort of malignancy and cancer, there are a number of cancer therapies available, including surgery, hormone therapy, radiation,

chemotherapy, immune targeting, stem cell transplantation, or a mix of these interventions [14].

Recently, significant progress has been made in many of the processes that lead to advances in BC treatment and how they are targeted (Figure 1). Combination techniques, such as multiple targeted therapies or "traditional" chemotherapy, including arsenic and platinum compounds, have a synergistic effect [15]. New treatment modalities, including biological molecules, pharmaceuticals, and immunomodulatory interventions, are used to decrease long-term survival periods for metastatic cancer while simultaneously raising rates of mortality, even in cases where the extraordinary therapy threshold has not been achieved [16]. Many in vitro and in vivo investigations regarding antioxidant therapies over the past few decades have shown that daily intake of a specific dosage of antioxidant nutrients is inversely associated with cancer risk while also improving the efficacy of treatment, despite the fact that randomized clinical trials have generated inconsistent findings that are believed to be an actual barrier for the widespread adoption of supplements with antioxidants in the treatment of cancer. These contradictory results can be caused by a variety of factors, such as dosage, synergy, bioavailability of used antioxidants, kind of cancer, patients' health status, lifestyle, tendency to utilize supplements, and research duration. Thus, to provide a secure and effective treatment, more regulated and clearly defined clinical studies using more recent techniques should be conducted. Thus, in order to develop a safe and efficient antioxidant supplementation system for the cancer treatment, more carefully planned and specified clinical trials using more recent methodologies need to be conducted. In a similar vein, in vivo research ought to take precedence over comprehensive studies into novel antioxidant compounds from algae and their purification techniques. The specific antioxidants found in the different organic and aqueous extracts that are currently showing antioxidant and cancer fighting abilities in vitro, in addition to their effects on the cell system and potential to enhance the effects of chemotherapy drugs, need further investigation [17]. Physical examination, imaging, especially mammography, and tissue biopsy are essential for the diagnosis of this cancer [18]. We aim to investigate the possible uses of algae, CSCs, probiotics, and nanoparticles in the medical treatment of BC according to the data provided in this introduction.

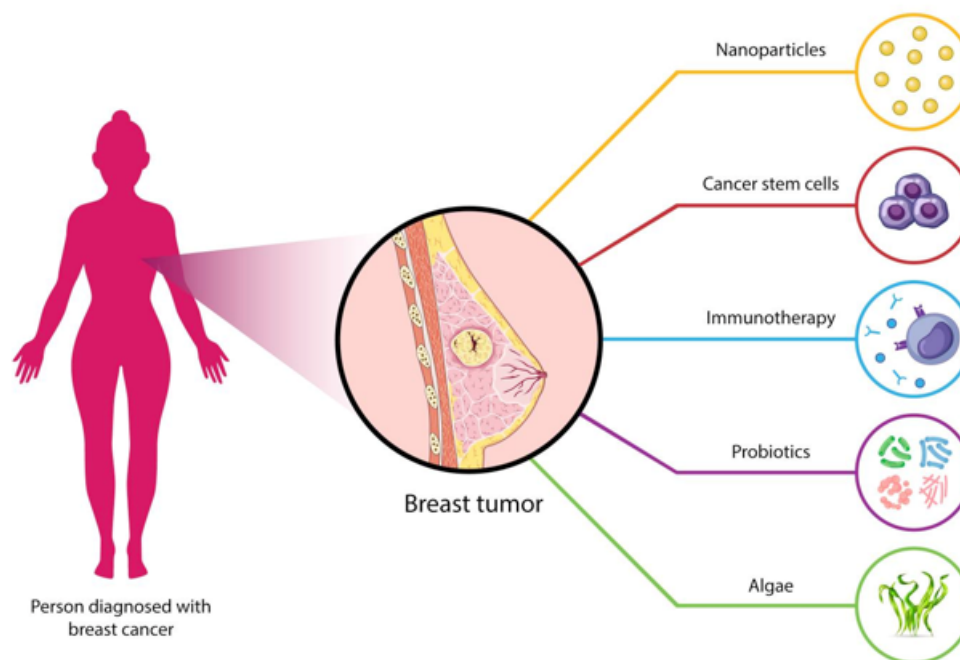


Figure 1: Current advancement and targeting strategies in breast cancer treatment.

Nanoparticles in Breast Cancer

Nanoparticles (NPs), which are microscopic particles of material measuring between 1-100nm in diameter, are used in nanotechnology [19]. The creation of nanomedicine agents through rapid progress in nanotechnology holds great promise for improving cancer therapy techniques [20] (Table 1). A new avenue in the treatment of cancer is presented by nanotechnology [21] (Fig. 2). These particles are highly modifiable for binding to cytoplasmic or nuclear receptor sites, the microenvironment, or the membranes of cancer cells [22]. In general, NPs can be classified as either inorganic or organic. Lipid and polymeric NPs are examples of organic NPs. Polymers comprise both homopolymers and copolymers. Homopolymer is categorized as a dendrimer, nanosphere, hydrogel nanocapsule, and nanocapsule. copolymer divided into polymerosomes and micelles. Lipid NPs comprised liposomes, solid lipid NPs, and micelles. Among the inorganic nanoparticles were carbon nanotube-ceramic NPs and metallic nanoparticle-fullerenes. Nanotechnology offers a more focused approach to addressing cancer-related challenges. Treating cancer disorders with a combination of nanocarriers and ligand targeting is a successful treatment approach. Cancer patients can benefit greatly from chemotherapy treatments, and using NPs for the treatment of cancer is additionally advantageous [23, 24]. Numerous NPs targeting malignant cells specifically while preserving healthy organs and tissues have been discovered

recently. Consequently, the application of targeted drug delivery systems mediated by them in the treatment of BC has shown promise. Apart from their ability to target malignancies and reduce adverse reactions, NPs have a number of particular characteristics making them appealing for use in cancer treatment. These features include low toxicity, good flexibility, and ease of preparation [25]. In addition to medications, genes, and imaging agents that can identify tumors, recent research has demonstrated that NPs offer a number of benefits for the treatment and diagnosis of tumors [20]. Gold NPs are one type of NPs used in the treatment of BC. One form of nanomaterials employed to treat BC is gold nanoparticles (Au NPs). These NPs readily penetrate and stay in tumor vasculature because of their increased permeability and retention effect since the openings found in these channels, which can vary in diameter between 100 nm and 2 μ m, are wider compared to the gaps that exist in the endothelium lining of healthy capillaries [26]. Alternatives that offer promise for the creation of novel anticancer medications are natural ingredients. Curcuma longa Linn, or Turmeric, is a plant whose rhizomes produce curcumin, also called diferuloylmethane, which is yellow in color. Curcuminoids and polyphenols are most abundant in the root of the plant. Due to its shown anti-inflammatory and antioxidant properties, curcumin is frequently utilized in culinary medicine and has been associated with conventional medicines. Kotan and associates originally revealed its anticancer effects

in lymphoma models and animal cells in 1985. In both in vivo and in vitro models, curcumin has anti-metastatic, anti-invasive, and antiangiogenic capabilities in addition to inhibiting BC cell proliferation and inducing apoptotic cell death [27]. Curcumin has also demonstrated potential in reversing the treatment-resistant behavior of BC cells resistant to doxorubicin (MDA-MB-231/DOX and MCF-7/DOX). Additionally, curcumin upregulated aldehyde dehydrogenase-1 and decreased the expression of the P-glycoprotein-mediated multidrug resistance gene, increasing the susceptibility of MCF-7 BC cells to paclitaxel. Regrettably, curcumin's limited water solubility and poor bioavailability restrict its medicinal use. Therefore, in order to increase curcumin's bioavailability and effectiveness, some research has looked into delivering it to BC cells using NPs [28-30]. Theranostics has a very promising future in the field of cancer therapy because of the effective advancement of dual-functionality NPs that are capable of monitoring/ imaging and treating a pharmaceutical disease. High multiplexibility makes it easier to combine tailored medication delivery at the right place to specifically kill tumor cells by conjugating ligands to NPs [31]. By reducing the pain associated

with conventional chemotherapy, addressing current clinical obstacles, and determining the direction of future therapeutic possibilities, NPs are being meticulously selected to significantly advance the goals of BC therapy and diagnostics [32]. Combining medications with NPs can have positive anti-tumor effects. For instance, doxorubicin and mannose-modified DOX-nanoparticles (DOX-AS-M-NPs) remarkably decreased the overall number of tumors in mice and effectively controlled the growth of tumors [33]. The directed responses of triple stimuli of gold nanorods mixed with hyaluronic acid and glutathione during the PDT-PTT protocol targeting MCF-7 cell lines were established by Xu et al. in a prospective investigation. The compounds had a circulatory half-life of 1.9 hours and an accumulation rate of approximately 12.8% in tumor tissue. Innovative technologies provide real-time intervention tracking, optimized heat generation, reduced adverse reactions, and unprecedented accuracy in targeting malignant cells. As the profession advances, combination and customization treatments are becoming commonplace, opening the door for an era in which cancer treatments will become as unique as each patient [34].

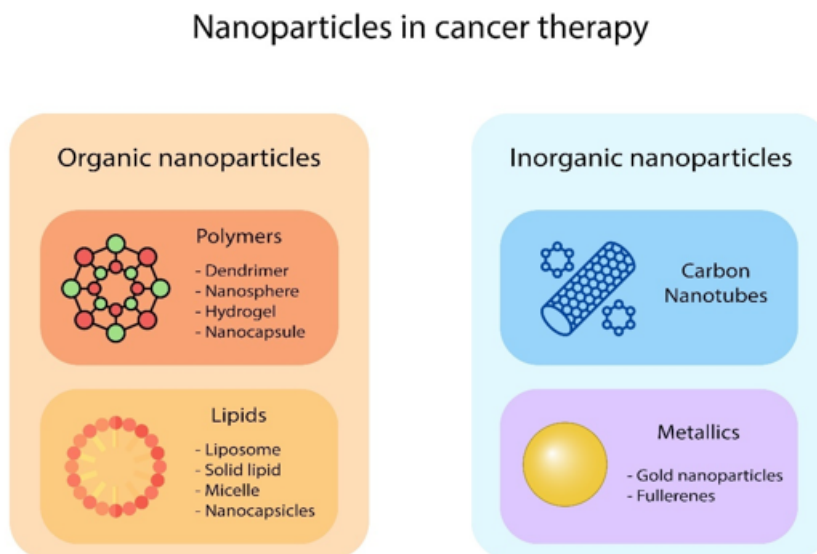


Figure 2: Current organic and inorganic nanoparticles used in cancer therapy.

Category	Subtype/example	Description and structure	Applications in cancer therapy	Advantages	Ref
Organic nanoparticles	Polymeric NPs	Made from natural/synthetic polymers; includes homopolymers and copolymers	Drug and gene delivery; chemotherapy enhancement; reversal of multidrug resistance	Biocompatibility, flexibility, and low toxicity	[20, 23, 24, 26]
	Homopolymer – Dendrimer	Branched synthetic polymers	Drug/gene loading, controlled release	High loading capacity, surface modifiability	[23, 24, 35]
	Homopolymer – Nanospheres	Solid matrix polymers	Sustained release of chemotherapeutics	Simple design, controlled kinetics	
	Homopolymer – Hydrogel nanocapsule	Hydrophilic 3D polymeric networks	Encapsulation of hydrophilic drugs	High water content, tunable release	[23, 26]
	Copolymer – Polymerosomes	Vesicle-like copolymer particles	Delivery of hydrophobic and hydrophilic drugs	High stability, dual loading	[23, 24]
	Copolymer – Micelles	Amphiphilic block copolymers self-assemble	Solubilization of hydrophobic anticancer drugs	Easy functionalization, tumor targeting	
	Lipid NPs – Liposomes	Phospholipid bilayer vesicles	Doxorubicin, paclitaxel delivery	Biodegradable, FDA-approved	[24, 25, 37]
	Solid lipid nanoparticles (SLNs)	Lipid core stabilized by surfactants	Controlled release of hydrophobic drugs	Biocompatibility, stability	[23, 24]
	Lipid micelles	Amphiphilic lipid assemblies	Paclitaxel, curcumin delivery	Enhanced solubility, tumor penetration	[24, 25, 38]
Inorganic NPs	Gold nanoparticles (AuNPs)	Metallic NPs with tunable size/shape	Tumor imaging, drug delivery, photothermal therapy	Enhanced permeability and retention (EPR) effect, real-time monitoring	[27, 39]
	Carbon nanotubes	Cylindrical carbon-based nanostructures	Gene/drug delivery, PTT, imaging	High loading, strong cell penetration	[23, 40]
	Fullerenes	Hollow spherical carbon cages	ROS generation, drug delivery	Antioxidant, multifunctional	[23, 41]
	Ceramic NPs	Silica/oxide-based nanostructures	Imaging, targeted drug release	High stability, low degradation	[23, 24, 42]
Natural product-based NPs	Curcumin-loaded NPs	Curcumin encapsulated in polymeric/lipid nanocarriers	Inhibition of proliferation, apoptosis induction, reversal of DOX resistance, synergy with paclitaxel	Improved solubility, bioavailability, and enhanced anti-BC effects	[29-31, 43]

Smart / Theranostic NPs	Dual-functionality NPs	NPs combining a drug & imaging agent	Simultaneous therapy + diagnosis (theranostics)	Precision targeting, real-time monitoring	[32, 39]
	Stimuli-responsive NPs	Gold nanorods + glutathione-hyaluronic acid (PDT-PTT)	Controlled therapy under external/internal triggers	Reduced side effects, targeted hyperthermia	[39, 44, 45]
Drug-Nanoparticle Conjugates	DOX-AS-M-NPs	Mannose-modified doxorubicin NPs	Reduced tumor volume, enhanced drug uptake	Targeted delivery, improved efficacy	[46, 47]

Table 1: Classification and applications of nanoparticles in cancer therapy.

Immunotherapy: A novel approach to treating breast cancer

In 1891, William B. Coley treated a patient with incurable cancer with an injection of streptococcal germs. He discovered that live or inactivated microorganisms could induce sarcoma remission, marking the inception of immunotherapy. Nevertheless, the relationship between immune cells and melanoma was not identified until the 1980s and 1990s, when researchers also developed the notion of cancer immunotherapy [39]. As an additional therapeutic option, cancer immunotherapy has advanced dramatically in recent years and rounds out the available treatment options. Unlike previous treatment approaches, immunotherapy’s main goals are to enhance the quality of life for those who are afflicted and stop the cancer from spreading metastatically [48]. Metastatic triple-negative breast cancer (TNBC), a kind of BC, is a disease that is aggressive, has a poor prognosis, and has few therapeutic choices. One intriguing new treatment option for this challenging condition is immunotherapy [49]. With the approval of autologous cellular immunotherapy, the field of cancer immunotherapy has lately experienced a major boost after many unsatisfactory attempts and clear clinical failures [50] (Table 2). Hematologic malignancies can now be effectively treated with cellular immunotherapy; however, outcomes in solid tumors have been less favorable due to their intrinsic heterogeneity and complex tumor microenvironment [51]. Adoptive cellular therapy (ACT), a different kind of immunotherapy that is quickly gaining popularity in clinical studies, entails separating T cells from a donor or patient, altering and/or growing them ex vivo, and then reintroducing them into the patient [52]. Adoptive cellular transfer treatment involves transferring specific HLA-matched allogeneic or autologous immune cells, which were successfully activated in vitro, to the patient for the purpose of triggering an anti-tumor immune response [51]. Innate lymphocytes known as natural killer (NK) cells are essential for eradicating cancerous cells and managing viral infections. The ability of NK cells to eliminate targeted cells without the need for prior sensitization was what first attracted their recognition [53]. Clinical efforts to apply adoptive NK cell transfer to solid tumors were motivated by the strategy’s

early success in treating hematologic malignancies. In vitro NK cells exhibit cytotoxicity against a broad spectrum of tumor cells belonging to solid cancer types. Adoptively transferred NK cells have also been shown to exhibit antitumor effects in vivo in preclinical xenograft mouse models of metastatic colorectal cancer, glioma, and ovarian cancer [54]. The CAR-NK cell idea was first studied preclinically utilizing the NK92 cell line, which was taken from a 50-year-old male patient with extranodal NK cell lymphoma (ENKL). Because of its relatively easy in vitro multiplication, the NK-92 cell line promises a potentially limitless source of CAR-NK cells. NK-92 cells must be exposed to radiation in order to decrease their ability to engraft in vivo since they originate from a malignant lineage [55]. It’s important to remember that CAR-NK cells might be an “off-the-shelf” product, even though allogeneic CAR-T cell therapies are still being researched [56].

The research of BC immunology has advanced significantly during the last decade (Figure 3). Twenty years ago, this cancer was thought to be non-immunogenic, and immunotherapy was not intended to be used to treat it. Today, we know that most patients with this cancer have evidence of an adaptive immune response to their cancer, either tumor-specific or peripheral blood-based [57]. Because tumor cells might develop new defense mechanisms to evade and outlive the immune response, immunotherapy has become a popular treatment option to fill in the holes in the current paradigm for treating BC. Thus, a better understanding of immune bypassing of malignant cells and monoclonal antibodies against PD-1 and PD-L1 can help in the diagnosis of this malignancy [58]. The impressive results of cancer immunotherapy in treating acute lung cancer, lymphoblastic leukemia, melanoma, and other cancers show that T cells can act as an exogenous tumor suppressor. The development of effective immunotherapy for people with BC starts to show results once it is underway. When it comes to treating individuals with triplenegative disease and advanced BC, monoclonal antibodies PD-11 or PD-1 (mAb) show the most promise. The objective response rate (ORR) in these investigations ranges from 12-19% [59]. At various stages of development and puberty, including postnatal puberty and

pregnancy, the breast stroma contains different kinds of immune cells, making immunity essential for healthy breast growth [60]. Since certain monoclonal antibodies (mAbs), including trastuzumab, have long been employed as therapeutic medicines for treating tumors in this malignancy, passive immunotherapy does not constitute a novel approach to treating this disease. Certain alternative methods, such as immune checkpoint inhibitors (ICIs) and antibody drug conjugates (ADCs), have garnered more interest recently as a preventative and therapeutic approach for this malignancy [57]. Appropriate antigen delivery systems and a thorough comprehension of the immune signaling pathways controlling reactions throughout the tumor microenvironment are necessary for effective therapeutic treatments [59]. With the development of immune validation at TNBC and immunological checkpoint inhibition (ICI) in solid tumors, immunotherapy has become more popular. Researchers are making progress by focusing on several safety checkpoints on multiple treatment lines for TNBC based on the accumulation of clinical studies. These involve programmed death inhibitors-1 (PD-1), antigen inhibitor-4 associated with cytotoxic T lymphocytes (CTLA-4), and other innovative immunotherapy techniques (e.g., cancer-testicular antigen (CTA), individual peptide vaccine, vaccine RNA, and modified T cells containing chimeric antigen receptor (CAR-T)) [61]. Since its molecular characteristics were discovered, BC has undergone significant change. It is now associated with immune markers (such as lymphocyte tumor penetration and PD-L1), genomic markers (such as PIK3CA, BRCA2, and BRCA1), and histochemical markers (such as iodine, PR, HER2 [URBB2], and protein proliferation markers Ki-67 [MKI67]). Typical treatments for metastatic BC comprise targeted medications such as PARP inhibitors, PI3K inhibitors, CDK4 and CDK6 inhibitors, and anti-PD-L1 immunotherapy, based on the tumor type and molecular profile. The diversity of available treatments reflects the complexity of modern care for this cancer [62]. Novel approaches to treating TNBC may be brought about by developments in immunotherapy, which stimulate the immune system of the host to eliminate tumor cells. Current research in this area focuses on combining NK cell therapy, PARP inhibitors, chemotherapy, and cancer vaccines with ICI. Furthermore, plant diets high in plant chemicals can efficiently modulate signaling molecules related to the safety checkpoint, such as PD-1/PD-L1, which is

why nutrients are frequently utilized in the TNBC treatment and prevention. Additionally, by specifically targeting cancer cells and controlling immune responses, for example, specially made NPs containing ligands on their surface can help deliver drugs more effectively. Furthermore, one effective strategy for overcoming multidrug resistance may be to use nanodrug delivery devices. However, a number of restrictions, such as inadequate therapeutic characteristics and poor oral biological access make their use complicated [63]. Although several novel treatment methods are currently in the clinical development stage, they are desperately needed for tackling the weakened anticancer immunity in TNBC. The IL-2 pathway agonist bempagaldesleukin, which specifically activates the IL-2b receptor to promote effector T cell growth while reducing proliferation of regulatory T cells, is one potential tactic. With an objective response rate (ORR) of 13.2%, the phase I/II PIVOT-02 study, which included 38 patients with metastatic TNBC who received bempagaldesleukin in addition to nivolumab, showed persistent responses regardless of PD-L1 expression rates. In TNBC, ongoing research is concentrating on more studies that combine bempagaldesleukin with chemotherapy and anti-PD-1/L1 treatments. The intratumoral toll-like receptor 9 (TLR9) agonist SD-101 is a different possible immunotherapeutic approach. It increases CD8+ T cell infiltration into malignancies by causing plasmacytoid dendritic cells (DCs) to release interferon- α and develop into antigen-presenting cells. As opposed to doxorubicin, paclitaxel, and cyclophosphamide alone, the I-SPY 2 study is now evaluating the possible pathological complete response (PCR) resulting from neoadjuvant SD-101 and pembrolizumab when combined with weekly paclitaxel following doxorubicin and cyclophosphamide [64-69]. According to experimental findings, 20% of TNBC patients have PD-L1, suggesting that this specific checkpoint protein could serve as a suitable therapeutic target for TNBC. Moreover, one of the processes in charge of controlling the expression of PD-L1 is the disappearance of PTEN. Consequently, agents that specifically target the PI3K pathway are expected to enhance antitumor immune responses, thereby potentially improving the efficacy of therapy for TNBC [70]. Immunotherapy in BC may face obstacles such as low immunogenicity, limited T-cell infiltration, and increased immunosuppression within the tumor microenvironment, which could hinder its effectiveness [71].

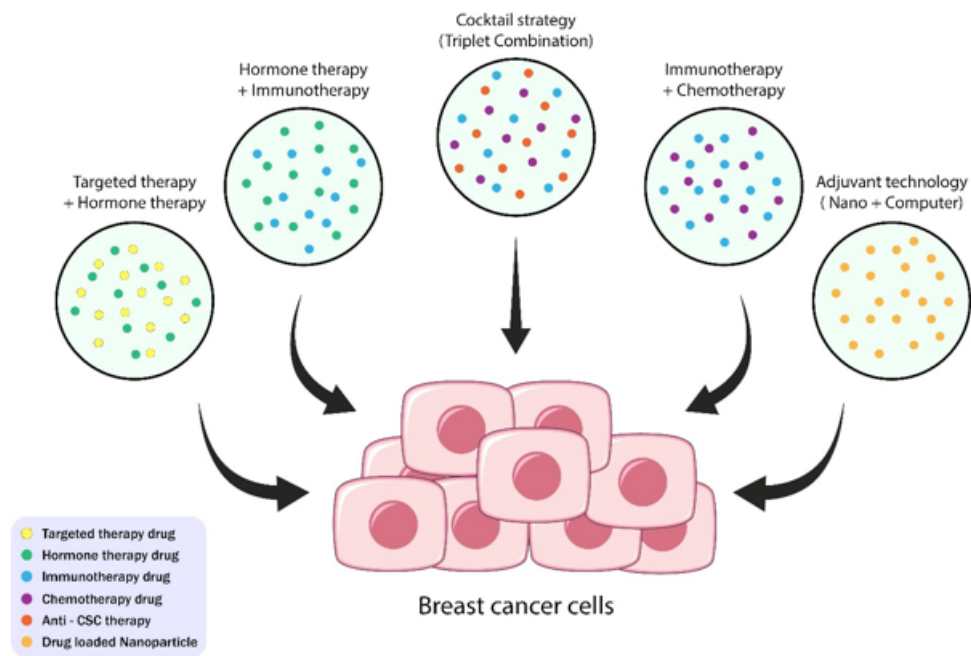


Figure 3: A schematic representation of the most recent breast cancer therapies. The sort and stage of malignancy have historically determined the type of therapy that is used. Combinations of several therapy modalities have also been employed more recently. Here is an outline of some of the most common therapy types and combination regimens.

Category	Details	Examples / key Notes	Ref
Checkpoint inhibition (ICI)	Antibodies targeting inhibitory receptors to restore T-cell activity	PD-L1, PD-1, CTLA-4 inhibitors; Objective Response Rate (ORR) in TNBC: 12–19%	[58, 60, 72]
Monoclonal antibodies (mAbs)	Passive immunotherapy targeting tumor antigens	Trastuzumab (HER2+ BC), antibody-drug conjugates (ADCs), PD-1/PD-L1 mAbs	[56, 58, 73]
Adoptive cell therapy	Infusion of patient/donor immune cells after expansion/modification	TILs, NK cells, CAR-T, CAR-NK	[51, 74, 75]
Natural killer (NK) cells	Cytotoxic lymphocytes that kill without sensitization	NK-92 cell line used in CAR-NK research; effective in hematologic & some solid tumors	[53, 55, 76, 77]
Combination approaches	Enhancing immunotherapy efficacy	Immunotherapy + chemotherapy, PARP inhibitors, nanocarriers, plant-derived compounds	[69, 78, 79]
Cancer stem cells (CSCs)	Role in BC	Drivers of metastasis, recurrence, drug/ radiation resistance, and immune evasion	[71, 72, 80, 81]
CSC markers and mechanisms	Surface and signaling targets	CD44, ALDH1, Notch, Wnt/β-catenin, Hedgehog; CSCs arrest in G0 phase → relapse/metastasis	[82-85]
Natural compounds and CSCs	Phytochemicals as immunomodulators	Polyphenols and plant-derived molecules disrupt CSC signaling & enhance sensitivity	[86-87]

Table 2: Current strategies of immunotherapy and cancer stem cell targeting in breast cancer.

Breast cancer and the function of cancer stem cells

The main reasons why cancer treatments fail include recurrence, heterogeneity, metastasis, resistance to radiation therapy and chemotherapy, and evasion of immune surveillance. All of these problems might be attributed to the characteristics of CSCs. CSCs can result in cancer recurrence, metastasis, resistance to multiple drugs, and radiation resistance due to their ability to stop at the G0 phase and produce new tumors. CSCs may thus be among the most appealing targets for cancer treatment [80]. The first solid proof of CSC existence was presented by Bonnet and Dick in 1997. They demonstrated that only CD34⁺CD38[−] cells isolated from patients with acute myeloid leukemia (AML) might result in hematological malignancies in non-obese diabetic/severe combined immunodeficient mice [88]. According to the CSC theory, they are in charge of the development, growth, and metastasis of tumors as well as treatment resistance. By selectively destroying active tumor cells, traditional cancer treatments like chemotherapy and radiation therapy may shrink tumors. They overlook CSCs that are inactive, which leads to relapse and resistance, which may even make CSCs more resistant [81]. Recently, a number of innovative therapeutic approaches have been developed for eliminating CSCs and altering the environment (niches) in which these cells are supported. Subtle changes in surface markers and alterations in signaling cascades make them attractive therapeutic targets. Researchers have identified several potential therapeutic targets for these cells, including the ABC transporter superfamily, DNA repair and detoxification enzymes, anti-apoptotic proteins, and oncogenic signaling cascades such as Hedgehog, Notch, EGFR, and Wnt/ β -catenin pathways. While certain treatment modalities are now successful in the removal of CSCs, others continue to be tested in clinical and preclinical environments [89] (Fig. 4). Some malignant cells are conceptually comparable to stem cells because they're capable of self-renewal and produce sizable numbers of nontumor cells. To clarify the genesis of BC cells, two theories have been put forth: either individual mammary cells may be reprogrammed, or the regulation of progenitor cells or MaSCs can be altered. Both ideas are not restrictive of one another, and both entail the accumulation of distinct mutational occurrences. CSCs, which are found in BC, have been linked to the development, course, and relapse of BC. Recent developments in single-cell sequencing have made it simpler to decipher the clonal evolution inside each breast tumor. Nevertheless, there haven't been many therapy studies conducted on this specific group of cancer cells [1]. The development of metastasis, drug resistance, and BC recurrence are all dependent on BC stem cells [86]. Recent studies have shown that CSCs are essential for targeting BC targets with treatment. With an emphasis on cancer immunotherapy, novel techniques for modifying CSCs as a targeted treatment for BC have been put forth [82]. There

could be CSCs, a fraction of cells capable of self-renewal, division, and both the onset and progression of tumor development, according to recent data. Moreover, it is believed that CSCs are responsible for drug resistance, metastasis, and cancer recurrence. Therefore, medications that target breast CSCs could be more successful medicines for managing metastases and recurrences as well as treating BC. Natural compounds, particularly phytochemicals, have garnered a lot of interest lately because of their key signaling pathways, wide immunological profile, and capacity to target many kinds of malignancies [83]. CSCs are a tiny but significant fraction of unidentified tumor cells, making up about 0.1–1% of total tumor cells. Breast cancer stem cells (BCSCs) have been shown to exist and play a part in the development, spread, progression, resistance to therapy, and recurrence of tumors. Over the past ten years, significant strides have been achieved in the identification, description, and isolation of this particular kind of cell in the research of BCSCs. Growing knowledge of the molecular elements and signaling pathways that sustain BCSC and its stem-like characteristics has made it easier to create targeted therapeutics for BCSCs. Currently available therapies for BCSC subpopulations focus on chemicals that disrupt the resting state of BCSCs and make them chemoresistant and radiation-sensitive, and they also concentrate on BCSC signaling pathways and constituents that preserve BCSC characteristics [84]. When exposed to hypoxia, Aldh1a1 expression is associated with increased HIF-1 α expression in BCSCs, but not HIF-2 α [90]. Stem cells function in a variety of ways when used to treat malignancies. One of the processes that allows hematopoietic stem cells (HSCs) to rapidly migrate to designated stem cell niches in the bone marrow is homing. After this, the grafts undergo a homing phase that is essential before specialized blood cell formation. The manufacturing of the matrix-degrading enzyme MMP-2 and the engagement of the stem cell receptor CXCR4 with endothelial cells through VLA-4/5, LFA-1, and CD44 are necessary for this process. It additionally relies on these receptors being in active contact. The tumor-tropic effect, which occurs when mesenchymal stem cells (MSCs) move into the tumor microenvironment in response to the production of CXCL16, CCL-25, SDF-1, and IL-6 by tumor cells and then differentiate into tumor-associated types of cells, further promotes tumor-stroma development [91]. Only by effectively resolving the challenges associated with the accurate and effective targeting of BCSCs can BC be eradicated. The majority of BCSC markers are not appropriate for targeting since they are also expressed in normal stem cells, despite the fact that they are broadly accessible. Of these markers, CD44 is the most prevalent one for cancer stem cells and is crucial for preserving stemness. Anti-CD44 antibodies have been successful in encouraging the terminal differentiation of CSCs in spite of a number of issues related to post-translational modification and CD44 splicing. Consequently, there is a notable decrease in both

the development of tumors and the occurrence of metastases [92-95]. The strategy of using drugs that disrupt the self-renewal process of specific stem cells is a preferred approach, although it poses a significant obstacle due to the common pathways between normal and tumor stem cells. The introduction of the CSC hypothesis will revolutionize our understanding of breast carcinogenesis and provide a rationale for the classification, detection, and prevention of this disease. In the case of metastatic BC, the implications are likely to be even broader, as no definitive treatment is currently available for this advanced stage of the disease. Recent research studies have demonstrated functional links between metastasis, stem cells, and cancer cell survival [96]. According to the CSC model, tumors are composed of a cellular hierarchy in which only CSCs have the ability to proliferate indefinitely, giving rise to other tumor cells that lack this ability. An increasing corpus of data supports this notion by indicating that CSCs may be linked to a worse prognosis by causing recurrence,

metastasis, and treatment failure [97]. Preclinical models should incorporate elements that target quiescent CSCs that persist locally or as micrometastases, even though surgery and supportive therapies are the first-line treatments for early-stage BC. This will help ensure the design of appropriate clinical trials [98]. Given the interconnectedness of the regulatory circuits controlling CSCs, eliminating this cell type may need a combination of targeted drugs [99]. Multidrug resistance, metastasis, radiation resistance, and recurrence of cancer are all triggered by CSCs since they have the ability to stop at G0 and produce new tumors. Therefore, one of the most promising therapies for treating cancer is the utilization of CSCs [80]. Because CSCs are extremely aggressive parts of the illness, TNBC represents one of the hardest cancers to treat. A new therapeutic approach might significantly improve TB treatment efficacy and survival rates while lowering the chance of a tumor recurrence [100].



Figure 4: Numerous therapies are aimed at eradicating cancer stem cells.

Probiotics: Definition and Special Role in Breast Cancer

The phrase “probiotics” has been around for a while, and Nobel laureate Eli Metchnikov recognized their immunomodulatory properties over a century ago. Probiotics are defined by the WHO and Food and Agriculture Organization (FAO) as living microorganisms (bacteria or yeasts) that improve the host’s health when administered in sufficient quantities (a dietary supplement in food) [101]. Probiotics are a variety of microorganisms, particularly lactic acid bacteria (LABs). Most species of *Lactobacillus*, several species of *Bifidobacteria*, *Enterococcus*, and *Streptococcus* are considered to be lactic acid bacteria. *Escherichia coli* Nissle 1917, a non-laboratory probiotic, was put to use for the treatment of intestinal infectious diseases. These bacterial species are mostly found in the human stomach. Only *Saccharomyces boulardii*, a non-pathogenic probiotic yeast, is utilized. Probiotics, both laboratory and non-laboratory, are widely recognized as harmless organisms that can be utilized for veterinary or medical applications without risk. Probiotics’ quantitative cytotoxic action makes them suitable as natural cancer treatment agents. Additionally, probiotics generate certain growth inhibitors that only affect cancer cells. A comprehensive overview of probiotics in breast BC therapy, organized by strain, biological activity, mechanisms, and evidence, is detailed in Table 3. It has been demonstrated that *Bifidobacterium animalis*, *Lactobacillus acidophilus*, *Lactocaseibacillus paracasei*, and *Bifidobacterium bifidum* prevent cancer cells from proliferating in MCF7 cells. *Lactobacillus helveticus* R389 was implicated in enhancing immunological enhancement, cytokines (such as IL-10 and IL-4), and reducing tumor cell development upon subcutaneous injection of 4T1 mouse breast adenocarcinoma cells into the BALB/c mice model [102]. Probiotics seem to have potential uses in the prevention, treatment, and management of problems related to BC. Their metabolic properties, immunomodulatory effects, and ability to disrupt the estrogen enterohepatic cycle can be leveraged for preventive benefits [103]. Because probiotics like *Lactobacillus* have an impact on gut microbiota and systemic immunoregulatory function, they may offer protection against BC. Studies conducted in vitro have demonstrated that probiotic treatment causes cancer cells to undergo apoptosis and stops them from proliferating. Probiotic therapy has been demonstrated in animal models to prevent tumor growth, shrink tumors, and have other positive effects [104]. Numerous investigations have demonstrated that probiotics’ metabiotics have anti-inflammatory and antioxidant properties, which underpin their anticancer benefits. Han et al. investigated the anti-inflammatory characteristics of the *Lactococcus lactis* NK34 strain in RAW 264.7 cells. Both cell growth and the generation of proinflammatory cytokines and nitric oxide were significantly reduced. The bacteria *Limosilactobacillus fermentum* SNR1 and *Limosilactobacillus mucosae* AN1

significantly reduced paw edema and increased the production of the anti-inflammatory cytokine IL-10 in comparison to the pro-inflammatory cytokine IL-6. Certain strains of *Lactocaseibacillus rhamnosus*, *Lactocaseibacillus paracasei*, and *Limosilactobacillus fermentum* have significant antioxidant activity, according to Chooruk et al. In another investigation, Yang et al. discovered that probiotics downregulate the metabolic enzymes that generate reactive oxygen species (ROS), glutathione (GSH), and butyrate. Probiotics may produce folate and protein bacteriocin with a low molecular weight, which has anticancer, anti-inflammatory, and immunomodulatory properties, according to an earlier study [105]. Probiotics are being suggested as possible strategies for triggering apoptosis, causing cell-cycle arrest, and preventing BC cell growth [106].

The effects of probiotics on BC were investigated in a number of in vivo and in vitro experiments. Moreno De Le Blanc et al. demonstrated that milk fermented by *Lactobacillus helveticus* R389 could control the immunological response in the mammary glands when localized BCs were present [162]. In mouse serum and mammary cells, rats fed and injected BC tumor cells fermented with milk *Lactobacillus helveticus* R389 show increased levels of IL-10 and lower levels of IL-6 cytokine, which inhibits breast tumor cells. In this regard, Yazdi and associates examined how oral treatment of *Lactobacillus acidophilus* affected the immune responses of BALB/c mice that received a BC cell transplant. The researchers suggest that a daily dosage of *Lactobacillus acidophilus* can increase the production of the immune-modulating cytokine IL-12 in splenocyte culture, even while the rate of tumor development in mice has reduced. Lacritz and associates showed that oral administration of the probiotic *Limosilactobacillus reuteri* prevented the early stages of BC in two mouse models: one with a genetic susceptibility to the disease, and the other fed a Western-style diet intended to cause mammary tumors. Additionally, Kassayová et al. observed that long-term treatment of *Lactobacillus plantarum* LS/07 efficiently combated BC through immunomodulation pathways [123]. In addition to medications, genes, and imaging agents that can identify tumors, recent research has demonstrated that NPs offer a number of benefits for tumor diagnosis and treatment [108]. In enough doses, probiotics—live, non-pathogenic microorganisms, have a significant positive impact on the health of the host. Whatever this definition, the reaction of dead probiotics and their metabolic secretions to various biological activities is equivalent to or greater than that of living probiotics. Acid resistance is one of probiotics’ primary qualities. Bile tolerance, mucous or epithelial cell adhesion resistance to antibiotics, the bile salt’s hydrolase potential for immunological stimulation, anti-carcinogenic and anti-disinfective properties against infections [109]. While the cytotoxic effects were less noticeable in normal HFF cells, the *Bacillus coagulans* supernatant

showed time- and concentration-dependent inhibitory effects on MCF 7 cells. The activation of apoptosis in malignancies was confirmed by accompanying flow cytometry data, downregulated expression of the anti-apoptotic BCL2 gene, and increased expression of the caspase-3 and caspase-9 genes [110]. It was discovered that *Saccharomyces boulardii* supernatant (SBS) had a stronger anticancer impact on MCF-7/mx cells than MCF-7. For the management of this kind of cancer in people, SBS is recommended as a possible anticancer medicine. It is highly advised that more research be done, particularly in vivo research, to discover more anticancer mechanisms of SBS against this malignancy. According to Zhang et al., *Lactocaseibacillus casei* and *Lactobacillus acidophilus* generate compounds that prevent MCF7 cell lines from proliferating [111]. In a metastatic mouse model of cancer, *Levilactobacillus brevis* (L. brevis) supplemented with selenium NPs decreased liver metastases and increased survival, according to Yazdi et al. In BALB/c mice with tumors, it also effectively stimulates immunological responses. Increased NK cell activity and greater quantities of T helper 1 cytokines, including IL-17 and IFN- γ , were among the immunological reactions [112].

Probiotic Strain/species	Type	Key mechanism(s)	Observed effects in cancer/breast cancer models	Experimental model/context	Ref
<i>Lactobacillus acidophilus</i>	LAB (bacteria)	Immunomodulation via IL-12, apoptosis induction, and cell-cycle arrest	↓ Tumor growth, ↑ IL-12 production in splenocytes	BALB/c mice with transplanted BC cells	[105, 113]
<i>Lactocaseibacillus paracasei</i>	LAB	Antioxidant, cytotoxicity on MCF7 cells	↓ Proliferation of BC cells, ROS regulation	In vitro (MCF7 cell line)	[103, 114]
<i>Lactobacillus rhamnosus</i>	LAB	Antioxidant activity, modulation of gut microbiota	Preventive effect in BC via immune regulation	In vitro, animal models	[103, 115]
<i>Lactobacillus helveticus R389</i>	LAB	Cytokine regulation (↑ IL-10, ↓ IL-6), immune response modulation	↓ Tumor cell growth, immunological enhancement	Mice (BALB/c) injected with 4T1 adenocarcinoma cells; milk-fermented models	[105, 116, 117]
<i>Lactococcus lactis NK34</i>	LAB	Anti-inflammatory (↓ NO, ↓ pro-inflammatory cytokines)	↓ Cell proliferation and inflammation	RAW 264.7 macrophage cells (in vitro)	[103, 118, 119]
<i>Limosilactobacillus mucosae AN1</i>	LAB	Immunomodulatory (↑ IL-10, ↓ IL-6), anti-inflammatory	↓ Paw edema, anti-inflammatory cytokine expression	Animal inflammatory models	[103, 120-122]
<i>Limosilactobacillus fermentum</i> (SNR1, others)	LAB	Antioxidant, anti-inflammatory, and bacteriocin production	↓ ROS, ↑ IL-10, anti-BC cytotoxicity	In vitro & in vivo	[104, 122]
<i>Lactiplantibacillus plantarum LS/07</i>	LAB	Long-term immunomodulation	Effective BC suppression through immune regulation	Mice, long-term probiotic administration	[105, 123, 124]
<i>Limolactobacillus reuteri</i>	LAB	Gut microbiota modulation, estrogen metabolism regulation	Prevention of early BC stages	Mice models (genetic predisposition & Western diet-induced)	[105, 125, 126]
<i>Bifidobacterium infantis</i>	LAB	Cytotoxicity, apoptosis induction	↓ Proliferation of MCF7 BC cells	In vitro (MCF7 cell line)	[127, 128]
<i>Bifidobacterium animalis</i>	LAB	Anti-proliferative effect	↓ BC cell proliferation	In vitro	[129, 130]

Bifidobacterium bifidum	LAB	Cytotoxic activity	Inhibition of MCF7 BC cell growth	In vitro	[110, 131]
Escherichia coli Nissle 1917	Non-lab probiotic bacterium	Modulation of gut microbiota, immune activity	Used in infectious diseases; potential role in cancer via immune modulation	Clinical, intestinal models	[132, 133]
Saccharomyces boulardii	Probiotic yeast	Non-pathogenic yeast, immune regulation	General gut health and immune system support	Widely used probiotic yeast	[132, 134]
Metabiotics (e.g., bacteriocins, folate, short-chain fatty acids)	Secondary metabolites of probiotics	Anti-inflammatory, antioxidant, anticancer	↓ ROS, ↑ GSH, apoptosis induction	In vitro & in vivo	[104, 135, 136]

Table 3: Probiotics in breast cancer prevention and therapy.

Algae

Both animals and human beings are immunomodulated by polysaccharides found in seaweeds and marine microalgae. Furthermore, these polysaccharides might have antioxidant, hypoglycemic, antiviral, anticancer, and anticoagulant qualities [137]. Algae can also be used to effectively deliver genetic medicines or chemotherapy to cancer patients. Certain algae extracts have been shown to have anticancer properties by increasing apoptosis and inhibiting tumor angiogenesis, metastasis, and cell proliferation. Algae are known to include a wide variety of natural components, such as terpenoids, proteins, sterols, cyclic polysulfide compounds, polyphenols, polysaccharides, macrolides, and other bioactive substances. These components have potent antiviral, cancer-preventing, and antioxidant properties. Moreover, algae could potentially be used for imaging-guided tumor treatment. Algae can be genetically engineered to target tumors and further enhance their physicochemical and biological activities. These developments have enormous potential to increase the use of algae in cancer treatment [138]. The nature and chemical characteristics of the algae bioactives serve as the primary basis for the method by which they work. According to Atashrazm et al., fucoidan inhibits lung cancer progression by delaying disease advancement, inducing cancer cell death, and exhibiting synergistic effects with anticancer chemotherapy agents [139]. Through the modification of signaling pathways, bioactive chemicals produced from algae are currently demonstrating anticancer effects by causing cell death and reducing cell proliferation [140].

Numerous studies have shown that natural chemicals exhibit a variety of biological characteristics and present intriguing avenues for the development of novel therapeutics. As a matter of fact, natural products possess anti-carcinogenic properties and have the ability to target multiple pathways that are implicated in BC, such as angiogenesis, apoptosis, differentiation, and proliferation of cells (141). Nowadays, natural ingredients represent the basis

of about 60% of all medications used to treat cancer. Around the world, seaweed has been eaten as food. Dietary fiber, minerals, polysaccharides, carbs, fats, proteins, and vitamins are abundant in them. According to recent research, seaweed may provide new anti-cancer medications [142]. Seaweed is a fascinating source of useful chemicals that have a range of health-promoting properties. Among these substances, polysaccharides have long piqued interest because of their potent anti-cancer properties. They increase the efficacy of traditional chemotherapy medications while having comparatively fewer negative effects on healthy human cells. Few studies, meanwhile, have provided an overview of the distinct anti-cancer properties and fundamental processes of seaweed polysaccharides (MAPs). As a result, the current review is on providing an update on the development of maps with anti-cancer capabilities, assessing their effectiveness, and elucidating their methods of action, including any implicated signaling pathways [143]. Research indicates that the use of Dunaliella salina algae in BC treatment lowers tumorization [144]. Plocamium cornutum, a red algae, is not cytotoxic to MCF-7 cells [145]. It has been hypothesized that methanol extract of Sargassum muticum (Japanese wireweed) (SMME) may, in a dose-and time-dependent manner, enhance apoptosis of human BC cells and decrease cancer cell proliferation based on current investigations on the effects of SMME on the proliferation of MCF-7 and MDA-MB-231 cell lines [146]. The food carotenoid, fucoxanthin (FX), is frequently present in diatoms and seaweed. The in vitro and in vivo studies demonstrated that FX and the non-acetylated metabolite fucoxanthinol (Fxol) both impede BC proliferation. The NF-κB signaling pathway is the primary mechanism believed to be responsible for the anti-angiogenic, anti-replication, and pro-apoptotic effects of fxol and Fx. Anti-cancer responses additionally involve other signaling molecules, such as CYP, ROS, MAPK, MMP2/9, MAPK, and CYP, that control the cancer metastasis, tumor microenvironment, oxidation, and carcinogenic metabolism [147]. East Asian cuisine has traditionally included fucoidan, an

edible algae. Recently, numerous pharmacological properties of polymers have been identified, including anti-inflammatory, antibacterial, antithrombotic, antiviral, and anticancer activities [148]. The information above suggests that chemicals found in algae may be helpful in the treatment of BC. A great source of antioxidant chemicals is microalgae. Since they are the product of microalgae defense mechanisms against stressors, carotenoids, polyphenols, fatty acids, phycobiliproteins, and vitamins are among the significant pharmacologically high-value metabolites that are commonly thought of as a basal load in microalgae. These bioactive substances possess both endogenous and ironic anti-cancer qualities in addition to demonstrated antioxidant capacity. Microalgal tetraterpenoids, for instance, have demonstrated encouraging anticancer activity in a variety of cell lines and are a strong source of antioxidants. Microalgal antioxidants are a valuable source of nutrients for human health since their activity is comparable to, or occasionally higher than, that of antioxidants derived from plants or animals [17]. Brown algae promote BC's apoptosis, suggesting a novel treatment strategy for this disease [149].

Discussion

Although the use of any of these new approaches can be effective in the treatment of BC, each approach has its own disadvantages. For instance, NPs are not entirely harmless substances; they may possess inherent cytotoxicity, which can occasionally have harmful effects on healthy tissues. These carrier systems can additionally put the patient in danger [150]. Expert opinions on medication delivery, the comparatively low T-cell infiltration in the majority of BCs for immunotherapy [151] and immunological rejection and disease recurrence when using CSCs are among the advantages and disadvantages of nanotechnologies for cancer patients and occupationally exposed workers.

Even while monotherapy works well for some BC patients, it can occasionally lose its efficacy as time passes and some patients become resistant to treatment. Even while monotherapy has shown promise, some patients—particularly those with metastatic disease—do not react well to treatment [152]. Enhancing the response rates of immunotherapies continues to pose a significant obstacle in the field of cancer treatment, especially when it comes to BC. It is imperative to investigate novel strategies that not only enable sufficient lymphocyte infiltration but also promote the production of fresh T-cell responses that combat the immunosuppressive tumor microenvironment, considering the generally low levels of T-cell infiltration seen in the majority of BC cases. The immunotherapy efficacy in patients with this cancer relies heavily on the development of such strategies [151]. Significant combinations are not expected to be limited solely to immune-to-immune pairings; numerous conventional

medications, including chemotherapy, radiotherapy, targeted therapy, or antitumor antibodies, have the potential to modulate the immune system, eliminate tumor cells in an immunogenic manner, or otherwise work in synergy with approved immune treatments like checkpoint blockade antibodies. Nevertheless, challenges related to toxicity, dosage, and sequencing pose significant obstacles, particularly for agonists. The primary obstacle in the realm of BC “combination immunotherapy” is the extensive array of potential pairings that likely surpass the number of patients and the capabilities of existing clinical trial infrastructures to evaluate them comprehensively. The most prioritized pairings will be those with distinct mechanisms and those that are backed by preclinical research incorporating a dependable immune pharmacodynamic biomarker [59].

New approaches to treating BC can result from developments in immunotherapy, which capitalizes on the host immune system's regeneration to destroy cancer cells. According to recent research, CSCs are crucial to the focused therapy of this illness. This malignancy has been emphasized for cancer immunotherapy, and new methods to alter CSCs can be employed as a targeted treatment. In the case of this malignancy, curcumin as a nanoparticle functions as an anti-invasive, anti-angiogenic, and anti-metastatic drug both in vitro and in vivo. It also slows cell proliferation and promotes death. The supernatants of *Bacillus coagulans* and *Saccharomyces boulardii* showed inhibitory impacts on MCF-7 cells that were both time-dependent and concentration-dependent. Brown algae could represent a novel treatment option for this malignancy since they promote apoptosis. TNBC is still the most difficult subtype of BC to eradicate nowadays. By altering the tumor microenvironment and stimulating anticancer immune responses, immunotherapy, nevertheless, can enhance the prognosis of TNBC patients, giving rise to optimism. The application of PD-1/PD-L1 monoclonal antibodies in TNBC immunotherapy has demonstrated encouraging outcomes in recent years and is steadily emerging as a key therapeutic strategy. For PD-L1-positive TNBC patients, atezolizumab is now a proven frontline treatment, according to the IMpassion130 research [61]. Future research might look into how probiotics and antibiotics can affect cancer therapy. For instance, research could be conducted on how 5-fluorouracil and probiotics work together for treating breast-metastatic colorectal cancer [153]. To improve treatment efficacy, future studies should concentrate on creating integrated platforms that incorporate several medicines and streamline the production of nanoparticles [154]. Potential applications of aptamer-based sensors for the future diagnosis and treatment of this type of BC have been described [155]. Researching the signaling pathways linked to BCSCs is believed to aid in the development of an effective illness therapy [156]. NK cells, macrophages (Macs), DCs, and T cells are the most widely used immune cell-based cancer therapies. Through

employing iPSCs as a framework for long-lasting genetic changes that affect suppressor signaling pathways and immune activation, such as chimeric antigen receptor transfer (CAR) or the removal of multipotent stem cells (iPSCs) and immunosuppressive inspection molecules, immune cells can be to exhibit antitumor activity. This is an essential tool for cancer treatment [157].

Combination treatment, which involves using two or more medications for the treatment of the disease, is a novel and exciting concept. As previously mentioned, monotherapies have shown some encouraging outcomes, although they are not always successful. Combination treatments, which integrate two or more medicinal substances or mono techniques, are being researched as a result. By focusing on several routes, the objective is to enhance patient satisfaction while lowering adverse effects and the emergence of resistance [158]. Microbiota's effect on BC could be compared to a two-sided blade. The study of the relationship between the host microbiota and this disease is still in its early stages and needs more clinical and preclinical studies, in contrast to its significance in pancreatic and gastrointestinal malignancies [159]. In recent times, researchers have made advancements in the field of medical treatment by combining probiotics with conventional therapies, including the use of TGF-beta blockade. In a clinical trial involving cancer patients, it was observed that resistance to the drug galunisertib, which acts as a TGF-beta inhibitor, developed over time. To enhance the effectiveness of galunisertib as a therapeutic option, Shi et al. conducted a study where they administered orally derived probiotics, specifically *Escherichia coli* Nissle 1917, to mice with 4T1 and H22 tumors. These mice were simultaneously undergoing TGF-beta blockade treatment [160]. It is anticipated that clinical trials investigating this approach will open the door to the potential use of probiotic bacteria as effective medication transporters for non-invasive cancer therapy in humans. The importance of probiotic balance in preserving general homeostasis has been highlighted in an increasing amount of research, which can have an effect on the effectiveness of cancer treatment. According to recent studies, probiotics could be used in innovative cancer therapies [161]. Proposed are future research approaches that prioritize the development of integrated platforms that integrate numerous therapies and optimize the manufacturing of NPs to improve therapeutic effectiveness.

Conclusions

BC is a significant worldwide health concern. Despite advancements in diagnosis and treatment, millions of women globally continue to be impacted by it. A multidisciplinary strategy for early detection, diagnosis, and treatment is essential due to the disease's complex etiology, which encompasses environmental as well as genetic variables. Key areas of contemporary research and potential therapeutic strategies include targeting CSCs, identifying and

eliminating CSCs may provide novel therapeutic opportunities, as these cells believed to contribute to tumor initiation, recurrence, and progression, utilizing probiotics to their maximum potential, investigating the impact of probiotics on the gut microbiota and its relationship to the development and metastasis of BC, exploiting the potential of algae and investigating the anti-cancer properties of various algal compounds and their capacity to enhance conventional therapies, employing nanomedicine, like developing medicine delivery systems with nanotechnology to improve treatment effectiveness and lessen negative effects. Despite these remarkable developments, additional study is required to completely comprehend the underlying causes of this malignancy and to provide more effective and accurate therapies. The main goals of future studies should be to discover new biomarkers, develop personalized treatment protocols, and improve patient outcomes. By combining scientific advances with clinical practice, we can move toward a time when this cancer is no longer a fatal disease.

Author Contributions: Conceptualization, A.M.A, H.K.; methodology, R.Y, E.A, A.S.; validation, S.A., T.K.; investigation, S.A.; resources.; T.K., A.S.; writing—original draft preparation, A.M.A.; review and editing, M.T.; supervision, A.M.A, H.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The relevant data are available from the corresponding author up-on reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BC - Breast Cancer

CSCs - Cancer Stem Cells

MaSCs - Mammary Stem Cells

DCIS - Ductal Carcinoma in Situ

DCs - Dendritic Cells

NPs - Nanoparticles

Au NPs - Gold Nanoparticles

ACT - Adoptive Cellular Therapy

ADCs - Antibody Drug Conjugates

ENKL - Extranodal NK Cell Lymphoma

PSCs - Multipotent Stem Cells

PCR - Pathological Complete Response

ROS - Reactive Oxygen Species ROS

References

1. Taurin S, Alkhalifa H. (2020) Breast cancers, mammary stem cells, and cancer stem cells, characteristics, and hypotheses. *Neoplasia* 22: 663-78.
2. Singleton A, Raeside R, Partridge SR, Hayes M, Maka K, et al. (2021) Co-designing a lifestyle focused text message intervention for women after breast cancer treatment: mixed methods study. *Journal of medical Internet research* 23: e27076.
3. Bergers G, Fendt SM. (2021) The metabolism of cancer cells during metastasis. *Nature Reviews Cancer* 21:162-80.
4. Majidpoor J, Mortezaee K. (2021) Steps in metastasis: an updated review. *Medical Oncology* 38: 3.
5. Gerstberger S, Jiang Q, Ganesh K. (2023) Metastasis. *Cell* 186:1564-79.
6. Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, et al. (2020) Breast cancer: Biology, biomarkers, and treatments. *International immunopharmacology* 84:106535.
7. Goff SL, Danforth DN. (2021) The role of immune cells in breast tissue and immuno therapy for the treatment of breast cancer. *Clinical breast cancer* 21: e63-e73.
8. Dianati-Nasab M, Salimifard K, Mohammadi R, Saadatmand S, Fararouei M, et al. (2024) Machine learning algorithms to uncover risk factors of breast cancer: insights from a large case control study. *Frontiers in Oncology* 13: 1276232.
9. do Nascimento RG, Otoni KM. (2020) Histological and molecular classification of breast cancer: what do we know? *Mastology* 30:1-8.
10. Smolarz B, Nowak AZ, Romanowicz H. (2022) Breast cancer—epidemiology, classification, pathogenesis and treatment (review of literature). *Cancers* 14: 2569.
11. Johnson KS, Conant EF, Soo MS. (2021) Molecular subtypes of breast cancer: a review for breast radiologists. *Journal of Breast Imaging* 3: 12-24.
12. Trayes KP, Cokenakes SE. (2021) Breast cancer treatment. *American family physician* 104:171-178.
13. Sudhakar A. (2009) History of cancer, ancient and modern treatment methods. *Journal of cancer science & therapy* 1:1.
14. He S, Li C, Zhang Q, Ding J, Liang XJ, et al. (2018) Tailoring platinum (IV) amphiphiles for self-targeting all in one assemblies as precise multimodal theranostic nanomedicine. *ACS nano* 12: 7272-81.
15. Mokhtari RB, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, et al. (2017) Combination therapy in combating cancer. *Oncotarget* 8: 38022.
16. Abbas Z, Rehman S. (2018) An overview of cancer treatment modalities. *Neoplasia* 1: 139-57.
17. Ferdous UT, Yusof ZNB. (2021) Medicinal prospects of antioxidants from algal sources in cancer therapy. *Frontiers in Pharmacology* 12: 593116.
18. Obeagu EI, Obeagu GU. (2024) Breast cancer: A review of risk factors and diagnosis. *Medicine* 103: e36905.
19. Lee J, Chatterjee DK, Lee MH, Krishnan S. (2014) Gold nanoparticles in breast cancer treatment: promise and potential pitfalls. *Cancer letters* 347: 46-53.
20. Aghebati Maleki A, Dolati S, Ahmadi M, Baghbanzadeh A, Asadi M, et al. (2020) Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. *Journal of cellular physiology* 235: 1962-1972.
21. Awasthi R, Roseblade A, Hansbro PM, Rathbone MJ, Dua K, et al. (2018) Nano-particles in cancer treatment: opportunities and obstacles. *Current drug targets* 19: 1696-709.
22. Haley B, Frenkel E. (2008) Nanoparticles for drug delivery in cancer treatment. *Urol Oncol* 26: 57-64.
23. Grewal IK, Singh S, Arora S, Sharma N. Polymeric nanoparticles for breast cancer therapy: A comprehensive review. *Biointerface Res Appl Chem.* 2021;11(4):11151.
24. Alqaraghuli HGJ, Kashanian S, Rafipour R. (2019) A review on targeting nanoparticles for breast cancer. *Current pharmaceutical biotechnology* 20:1087-107.
25. Liyanage PY, Hettiarachchi SD, Zhou Y, Ouhtit A, Seven ES, et al. (2019) Nanoparticle mediated targeted drug delivery for breast cancer treatment. *Biochimica et Biophysica Acta (BBA) Reviews on Cancer* 1871: 419-433.
26. Kah JCY, Wong KY, Neoh KG, Song JH, Fu JWP, et al. (2009) Critical parameters in the pegylation of gold nanoshells for biomedical applications: an in vitro macrophage study. *Journal of drug targeting* 17:181-93.
27. Adahoun MaA, Al-Akhras M-AH, Jaafar MS, Bououdina M. (2017) Enhanced anticancer and antimicrobial activities of curcumin nanoparticles. *Artificial cells, nanomedicine, and biotechnology* 45: 98-107.
28. Bhawana, Basniwal RK, Buttar HS, Jain V, Jain N, et al. (2011) Curcumin nanoparticles: preparation, characterization, and antimicrobial study. *Journal of agricultural and food chemistry* 59: 2056-61.
29. Yen F-L, Wu TH, Tzeng C-W, Lin L-T, Lin C-C, et al. (2010) Curcumin nanoparticles improve the physicochemical properties of curcumin and effectively enhance its antioxidant and antihepatoma activities. *Journal of agricultural and food chemistry* 58:7376-82.
30. Liu J, Xu L, Liu C, Zhang D, Wang S, et al. (2012) Preparation and characterization of cationic curcumin nanoparticles for improvement of cellular uptake. *Carbohydrate polymers* 90:16-22.
31. Thakur V, Kutty RV. (2019) Recent advances in nanotheranostics for triple negative breast cancer treatment. *Journal of Experimental & Clinical Cancer Research* 38: 430.
32. Mirza Z, Karim S. (2021) Nanoparticles-based drug delivery and gene therapy for breast cancer: Recent advancements and future challenges. *Semin Cancer Biol* 69: 226-237.
33. Liu Y, Zhang D, Zhang Z, Liang X, Yang X, et al. (2024) Multifunctional nanoparticles inhibit tumor and tumor associated macrophages for triple-negative breast cancer therapy. *Journal of colloid and interface science* 657: 598-610.
34. Nag S, Mitra O, Tripathi G, Adur I, Mohanto S, et al. (2024) Nanomaterials assisted Photothermal Therapy for Breast Cancer: State of the Advances and Future Perspectives. *Photodiagnosis and Photodynamic Therapy* 45: 103959.

35. Jaimini M, Kothari A. (2012) Sustained release matrix type drug delivery system: A re-view. *Journal of Drug Delivery and Therapeutics* 2:142-148.
36. Li Q, Li X, Bury E, Lackey K, Koh A, et al. (2023) Hydration-Induced Void-Containing Hydrogels for Encapsulation and Sustained Release of Small Hydrophilic Molecules. *Advanced Functional Materials* 33: 2301025.
37. Abaza T, Mohamed EE, Zaky MY. (2025) Lipid nanoparticles: a promising tool for nucleic acid delivery in cancer immunotherapy. *Med Oncol* 42: 409.
38. Wei Y, Wei Y, Sheng L, Ma J, Su Z, et al. (2023) Construction of Curcumin and Paclitaxel Co-Loaded Lipid Nano Platform and Evaluation of Its Anti-Hepatoma Activity in vitro and Pharmacokinetics in vivo. *Int J Nanomedicine* 18: 2087-107.
39. Wang Y, Wang M, Wu HX, Xu RH. (2021) Advancing to the era of cancer immunotherapy. *Cancer Communications* 41: 803-829.
40. Zare H, Ahmadi S, Ghasemi A, Ghanbari M, Rabiee N, et al. (2021) Carbon Nanotubes: Smart Drug/Gene Delivery Carriers. *Int J Nanomedicine* 16:1681-706.
41. Faraj A, Awlqadr FH, Ahmed A, Amin HH, Haidar Z, et al. (2025) Innovative therapeutic potential of C60 fullerene in nanomedicine. *Journal of Drug Delivery Sci-ence and Technology* 113: 107315.
42. Ilhan-Ayisigi E, Yesil-Celiktas O. (2018) Silica-based organic-inorganic hybrid nanoparticles and nanoconjugates for improved anticancer drug delivery. *Eng Life Sci* 18: 882-92.
43. Bhawana, Basniwal RK, Buttar HS, Jain VK, Jain N, et al. (2011) Curcumin nanoparticles: preparation, characterization, and antimicrobial study. *Journal of agricultural and food chemistry* 59: 2056-61.
44. Xu W, Qian J, Hou G, Wang Y, Wang J, et al. (2019) A dual targeted hyaluronic acid-gold nanorod platform with triple-stimuli responsiveness for photodynamic/photothermal therapy of breast cancer. *Acta biomaterialia* 83: 400-13.
45. Imantay A, Mashurov N, Zhaisanbayeva BA, Mun EA. (2025) Doxorubicin-Conjugated Nanoparticles for Potential Use as Drug Delivery Systems. *Nanomaterials* 15: 133.
46. Nag S, Mitra O, Tripathi G, Adur I, Mohanto S, et al. (2024) Nanomaterials assisted photothermal therapy for breast cancer: State of the art advances and future perspectives. *Photodiagnosis and Photodynamic Therapy* 45:103959.
47. Khan KA, Chandra J, Gupta G, Ghazwani M, Hani U, et al. (2025) Mannose Directed Nanoparticle Delivery Systems Enhancing Targeted Cancer Treatment. *Journal of Drug Delivery Science and Technology* 112: 107283.
48. Schuster M, Nechansky A, Kircheis R. (2006) Cancer immunotherapy. *Biotechnology Journal: Healthcare Nutrition Technology* 1: 138-47.
49. Dvir K, Giordano S, Leone JP. (2024) Immunotherapy in Breast Cancer. *International Journal of Molecular Sciences* 25: 7517.
50. Farkona S, Diamandis EP, Blasutig IM. (2016) Cancer immunotherapy: the beginning of the end of cancer? *BMC medicine* 14: 73.
51. Tan S, Li D, Zhu X. (2020) Cancer immunotherapy: Pros, cons and beyond. *Biomedicine & Pharmacotherapy* 124:109821.
52. Kirtane K, Elmariah H, Chung CH, Abate-Daga D. (2021) Adoptive cellular therapy in solid tumor malignancies: review of the literature and challenges ahead. *Journal for immunotherapy of cancer* 9: 7.
53. Berrien-Elliott MM, Jacobs MT, Fehniger TA. (2023) Allogeneic natural killer cell therapy. *Blood* 141: 856-868.
54. Liu S, Galat V, Galat Y, Lee YKA, Wainwright D, et al. (2021) NK cell based cancer immunotherapy: from basic biology to clinical development. *Journal of hematology & oncology* 14:1-17.
55. Wrona E, Borowiec M, Potemski P. (2021) CAR-NK cells in the treatment of solid tumors. *International journal of molecular sciences* 22: 5899.
56. Albinger N, Hartmann J, Ullrich E. (2021) Current status and perspective of CAR-T and CAR-NK cell therapy trials in Germany. *Gene therapy* 28: 513-527.
57. Arab A, Yazdian-Robati R, Behravan J. (2020) HER2 positive breast cancer immunotherapy: A focus on vaccine development. *Archivum immunologiae et therapiae Experimentalis* 68:1-18.
58. Alshehri B. (2021) Immunotherapy: New insights in breast cancer treatment. *Human Antibodies* 29:193-202.
59. Vonderheide RH, Domchek SM, Clark AS. (2017) Immunotherapy for breast cancer: what are we missing? *Clinical Cancer Research* 23: 2640- 2646.
60. Henriques B, Mendes F, Martins D. (2021) Immunotherapy in breast cancer: when, how, and what challenges? *Biomedicines* 9:1687.
61. Zhu Y, Zhu X, Tang C, Guan X, Zhang W, et al. (2021) Progress and challenges of immunotherapy in triple negative breast cancer. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer* 1876: 188593.
62. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G, et al. (2021) Epidemiology and risk factors. *Breast Cancer Lancet* 397: 1750-1769.
63. Kudelova E, Smolar M, Holubekova V, Hornakova A, Dvorska D, et al. (2022) Genetic heterogeneity, tumor microenvironment and immunotherapy in triple negative breast cancer. *International Journal of Molecular Sciences* 23:14937.
64. Keenan TE, Tolaney SM. (2020) Role of immunotherapy in triple-negative breast cancer. *Journal of the National Comprehensive Cancer Network* 18: 479-489.
65. Brufsky A, Kim S-B, Zvirbulis Z, Dirix LY, Eniu AE, et al. (2021) Phase II COLET study: Atezolizumab (A)+ cobimetinib (C)+ paclitaxel (P)/nab-paclitaxel (nP) as first-line (1L) treatment (tx) for patients (pts) with locally advanced or metastatic triple negative breast cancer (mTNBC). *Ann Oncol* 32: 652-660.
66. Charych DH, Hoch U, Langowski JL, Lee SR, Addepalli MK, et al. (2016) NKTR-214, an engineered cytokine with biased IL2 receptor binding, increased tumor exposure, and marked efficacy in mouse tumor models. *Clinical Cancer Research* 22: 680-90.
67. Diab A, Hurwitz ME, Cho DC, Papadimitrakopoulou V, Curti BD, et al. (2018) NKTR-214 (CD122-biased agonist) plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of PIVOT. *J Clin Oncol* 36: 3006.
68. Benteibibel S-E, Hurwitz ME, Bernatchez C, Haymaker C, Hudgens CW, et al. (2019) A first-in-human study and biomarker analysis of NKTR-214, a novel IL2R β -biased cytokine, in patients with advanced or metastatic solid tumors. *Cancer Discovery* 9: 711-721.
69. Ribas A, Medina T, Kummar S, Amin A, Kalbasi A, et al. (2018) SD-101 in combination with pembrolizumab in advanced melanoma: results of a phase Ib, mul-ticenter study. *Cancer discovery* 8:1250-1257.
70. Jia H, Truica CI, Wang B, Wang Y, Ren X, et al. (2017) Immunotherapy for triple-negative breast cancer: Existing challenges and exciting

- prospects. *Drug re-sistance updates* 32:1-15.
71. Basu A, Ramamoorthi G, Jia Y, Faughn J, Wiener D, et al. (2019) Immunotherapy in breast cancer: Current status and future directions. *Advances in cancer re-search* 143: 295-349.
 72. Arab A, Yazdian-Robati R, Behravan J. (2020) HER2-positive breast cancer immuno-therapy: a focus on vaccine development. *Archivum immunologiae et therapias Experimentalis* 68: 2.
 73. Agostinetti E, Montemurro F, Puglisi F, Criscitiello C, Bianchini G, et al. (2022) Immunotherapy for HER2-Positive Breast Cancer: Clinical Evidence and Future Perspectives. *Cancers (Basel)* 14: 2136.
 74. Farkona S, Diamandis EP, Blasutig IM. (2016) Cancer immunotherapy: the beginning of the end of cancer? *BMC medicine* 14: 73.
 75. Fang KK, Lee JB, Zhang L. (2022) Adoptive Cell Therapy for T-Cell Malignancies. *Cancers (Basel)* 15: 94.
 76. Kirtane K, Elmariam H, Chung CH, Abate-Daga D. (2021) Adoptive cellular therapy in solid tumor malignancies: review of the literature and challenges ahead. *Journal for immunotherapy of cancer* 9: e002723.
 77. Liu S, Galat V, Galat4 Y, Lee YKA, Wainwright D, et al. (2021) NK cell-based cancer immunotherapy: from basic biology to clinical development. *Journal of hematology & oncology* 14: 7.
 78. Zafar T, Naik AQ, Kumar M, Shrivastava VK. (2022) Epidemiology and risk factors of breast cancer. *Breast cancer: From bench to personalized medicine* 3-29.
 79. Qureshi MJ, Narde GK, Ahuja A, Meenakshi DU, Al Balushi K, et al. (2025) Combination Therapy Using Phytochemicals and PARP Inhibitors in Hybrid Nanocarriers: An Optimistic Approach for the Management of Colon Cancer. *International Journal of Molecular Sciences* 26: 7350.
 80. Yang L, Shi P, Zhao G, Xu J, Peng W, et al. (2020) Targeting cancer stem cell pathways for cancer therapy. *Signal transduction and targeted therapy* 5: 8.
 81. Han L, Shi S, Gong T, Zhang Z, Sun X, et al. (2013) Cancer stem cells: therapeutic implications and perspectives in cancer therapy. *Acta Pharmaceutica Sinica B* 3: 65-75.
 82. Ghasemi F, Sarabi PZ, Athari SS, Esmaeilzadeh A. (2019) Therapeutics strategies against cancer stem cell in breast cancer. *The international journal of biochemistry & cell biology* 109: 76-81.
 83. Dandawate PR, Subramaniam D, Jensen RA, Anant S. (2016) Targeting cancer stem cells and signaling pathways by phytochemicals: Novel approach for breast cancer therapy. *Semin Cancer Biol* 41: 192-208.
 84. Zhang X, Powell K, Li L. (2020) Breast cancer stem cells: biomarkers, identification and isolation methods, regulating mechanisms, cellular origin, and beyond. *Cancers* 12: 3765.
 85. Emami Nejad A, Najafgholian S, Rostami A, Sistani A, Shojaeifar S, et al. (2021) The role of hypoxia in the tumor microenvironment and development of cancer stem cell: a novel approach to developing treatment. *Cancer Cell International* 21: 62.
 86. Khan S, Suryavanshi M, Kaur J, Nayak D, Khurana A, et al. (2021) Stem cell therapy: A paradigm shift in breast cancer treatment. *World journal of stem cells* 13: 841.
 87. Chan MM, Chen R, Fong D. (2018) Targeting cancer stem cells with dietary phytochemical - Repositioned drug combinations. *Cancer Lett* 433: 53-64.
 88. Dawood S, Austin L, Cristofanilli M. (2014) Cancer stem cells: implications for cancer therapy. *Oncology (Williston Park)* 28: 1101-7.
 89. Chen K, Huang Y-h, Chen J-l. (2013) Understanding and targeting cancer stem cells: therapeutic implications and challenges. *Acta Pharmacologica Sinica* 34: 732-40.
 90. Emami Nejad A, Najafgholian S, Rostami A, Sistani A, Shojaeifar S, et al. (2021) The role of hypoxia in the tumor microenvironment and development of cancer stem cell: a novel approach to developing treatment. *Cancer Cell International* 21: 1-26.
 91. Debela DT, Muzazu SG, Heraro KD, Ndalama MT, Mesele BW, et al. (2021) New approaches and procedures for cancer treatment: Current perspectives. *SAGE open medicine* 9: 20503121211034366.
 92. Naor D, Sionov RV, Ish-Shalom D. (1997) CD44: structure, function and association with the malignant process. *Advances in cancer research* 71: 241-319.
 93. Thapa R, Wilson GD. (2016) The importance of CD44 as a stem cell biomarker and therapeutic target in cancer. *Stem Cells Int* 2016: 2087204.
 94. Charrad R-S, Li Y, Delpech B, Balitrand N, Clay D, et al. (1999) Ligation of the CD44 adhesion molecule reverses blockage of differentiation in human acute myeloid leukemia. *Nature medicine* 5: 669-76.
 95. Saeg F, Anbalagan M. (2018) Breast cancer stem cells and the challenges of eradication: a review of novel therapies. *Stem Cell Investig* 5: 39.
 96. Charafe-Jauffret E, Monville F, Ginestier C, Dontu G, Birnbaum D, et al. (2008) Cancer stem cells in breast: current opinion and future challenges. *Pathobiology* 75: 75-84.
 97. Carrasco E, Álvarez PJ, Prados J, Melguizo C, Rama AR, et al. (2014) Cancer stem cells and their implication in breast cancer. *European journal of clinical investigation* 44: 678-87.
 98. Al-Ejeh F, Smart CE, Morrison BJ, Chenevix-Trench G, López JA, et al. (2011) Breast cancer stem cells: treatment resistance and therapeutic opportunities. *Carcinogenesis* 32: 650-8.
 99. Liu S, Wicha MS. (2010) Targeting breast cancer stem cells. *Journal of clinical oncology* 28: 4006.
 100. Ghazimoradi MH, Pakravan K, Khalafizadeh A, Babashah S. (2024) TET1 regulates stem cell properties and cell cycle of Cancer stem cells in triple negative breast cancer via DNA demethylation. *Biochemical Pharmacology* 219: 115913.
 101. Mendoza L. (2019) Potential effect of probiotics in the treatment of breast cancer. *Oncology reviews* 13: 422.
 102. Malik SS, Saeed A, Baig M, Asif N, Masood N, et al. (2018) Anticarcinogenicity of microbiota and probiotics in breast cancer. *International journal of food properties* 21: 655-66.
 103. Ranjbar S, Seyednejad SA, Azimi H, Rezaeizadeh H, Rahimi R, et al. (2019) Emerging roles of probiotics in prevention and treatment of breast cancer: a comprehensive review of their therapeutic potential. *Nutrition and Cancer* 71: 1-12.
 104. Mokbel K, Mokbel K. (2024) Harnessing micronutrient power: vitamins, antioxidants and probiotics in breast cancer prevention. *Anticancer Research* 44: 2287-2295.
 105. Sankarapandian V, Venmathi Maran BA, Rajendran RL, Jogalekar MP, Guruna-garajan S, et al. (2022) An update on the effectiveness of probiotics in the prevention and treatment of cancer. *Life* 12: 59.
 106. Jia Y, Feng C, Sun S, Li C, Li J, et al. (2024) Cheese intake, probiotics and breast cancer: A Mendelian randomization analysis. *Journal of Functional Foods* 119: 106352.

107. Laborda-Illanes A, Sanchez-Alcoholado L, Dominguez-Recio ME, Jimenez-Rodriguez B, Lavado R, et al. (2020) Breast and gut microbiota action mechanisms in breast cancer pathogenesis and treatment. *Cancers* 12: 2465.
108. Aghebati-Maleki A, Dolati S, Ahmadi M, Baghbanzadeh A, Asadi M, et al. (2020) Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. *J Cell Physiol* 235: 1962-1972.
109. Legesse Bedada T, Feto TK, Awoke KS, Garedew AD, Yifat FT, et al. (2020) Probiotics for cancer alternative prevention and treatment. *Biomed Pharmacother* 129: 110409.
110. Dolati M, Tafvizi F, Salehipour M, Movahed TK, Jafari P, et al. (2021) Inhibitory effects of probiotic *Bacillus coagulans* against MCF7 breast cancer cells. *Iran J Microbiol* 13: 839-847.
111. Bedada TL, Feto TK, Awoke KS, Garedew AD, Yifat FT, et al. (2020) Probiotics for cancer alternative prevention and treatment. *Biomedicine & pharmacotherapy* 129: 110409.
112. Motevaseli E, Dianatpour A, Ghafouri-Fard S. (2017) The role of probiotics in cancer treatment: emphasis on their in vivo and in vitro anti-metastatic effects. *International journal of molecular and cellular medicine* 6: 66.
113. Yazdi MH, Soltan Dallal MM, Hassan ZM, Holakuyee M, Agha Amiri S, et al. (2010) Oral administration of *Lactobacillus acidophilus* induces IL-12 production in spleen cell culture of BALB/c mice bearing transplanted breast tumour. *Br J Nutr* 104: 227-32.
114. Kis B, Pavel IZ, Avram S, Moaca EA, Herrero San Juan M, et al. (2022) Anti-microbial activity, in vitro anticancer effect (MCF-7 breast cancer cell line), antiangiogenic and immunomodulatory potentials of *Populus nigra* L. buds extract. *BMC Complement Med Ther* 22: 74.
115. Han SK, Shin YJ, Lee DY, Kim KM, Yang SJ, et al. (2021) *Lactobacillus rhamnosus* HDB1258 modulates gut microbiota-mediated immune response in mice with or without lipopolysaccharide-induced systemic inflammation. *BMC Microbiol* 21: 146.
116. Thoda C, Touraki M. (2025) Molecular Mechanisms of Probiotic Action Against Gastro-intestinal Cancers. *Int J Mol Sci* 26: 7857.
117. Méndez Utz VE, Pérez Visiuk D, Perdigon G, de Moreno de LeBlanc A. (2021) Milk fermented by *Lactobacillus casei* CRL431 administered as an immune adjuvant in models of breast cancer and metastasis under chemotherapy. *Appl Microbiol Biotechnol* 105: 327-340.
118. Han KJ, Lee NK, Park H, Paik HD. (2015) Anticancer and Anti-Inflammatory Activity of Probiotic *Lactococcus lactis* NK34. *J Microbiol Biotechnol* 25: 1697-701.
119. Lu Y, Wu Y, Pan L, Wang J, Tang R, et al. (2024) In Vitro screening of lactic acid bacteria with RAW264. 7 macrophages and the immunoregulatory mechanism. *Processes* 12: 903.
120. Oladejo BO, Adeboboye CF, Adiji PI, Adebolu TT. (2023) Cytokine-mediated immuno regulatory activity of *Lactobacillus* species in a carrageenan-induced acute inflammation model. *BioTechnologia (Pozn)* 104: 53-63.
121. Wang Q, Fang Z, Li L, Wang H, Zhu J, et al. (2022) *Lactobacillus mucosae* exerted different antiviral effects on respiratory syncytial virus infection in mice. *Front Microbiol* 13: 1001313.
122. Ayyanna R, Ankaiah D, Arul V. (2018) Anti-inflammatory and Antioxidant Properties of Probiotic Bacterium *Lactobacillus mucosae* AN1 and *Lactobacillus fermentum* SNR1 in Wistar Albino Rats. *Front Microbiol* 14: 9:3063.
123. Kassayová M, Bobrov N, Strojny L, Orendáš P, Demečková V, et al. (2016) Anticancer and Immunomodulatory Effects of *Lactobacillus plantarum* LS/07, Inulin and Melatonin in NMU-induced Rat Model of Breast Cancer. *Anticancer Res* 36: 2719-28.
124. Štofilová J, Szabadosová V, Hrčková G, Salaj R, Bertková I, et al. (2015) Co-administration of a probiotic strain *Lactobacillus plantarum* LS/07 CCM7766 with prebiotic inulin alleviates the intestinal inflammation in rats exposed to N,N-dimethylhydrazine. *International Immunopharmacology* 24: 361-368.
125. Qi X, Yun C, Pang Y, Qiao J. (2021) The impact of the gut microbiota on the reproductive and metabolic endocrine system. *Gut Microbes* 13: 1-21.
126. Lakritz JR, Poutahidis T, Levkovich T, Varian BJ, Ibrahim YM, et al. (2014) Beneficial bacteria stimulate host immune cells to counteract dietary and genetic predisposition to mammary cancer in mice. *Int J Cancer* 135: 529-40.
127. Jamalzadeh L, Ghafoori H, Aghamaali M, Sariri R. (2017) Induction of Apoptosis in Human Breast Cancer MCF-7 Cells by a Semi-Synthetic Derivative of Artemisinin: A Caspase-Related Mechanism. *Iran J Biotechnol* 15:157-165.
128. Ardehsir RA, Moarefvand K. (2025) Selective apoptosis induction by antimicrobial pep-tide TP4 in MCF-7 breast cancer cells. *Sci Rep* 15:15061.
129. Asadollahi P, Ghanavati R, Rohani M, Razavi S, Esghaei M, et al. (2020) Anticancer effects of *Bifidobacterium* species in colon cancer cells and a mouse model of carcinogenesis. *PLoS One* 15: e0232930.
130. Ren Z, Chen S, Lv H, Peng L, Yang W, et al. (2022) Effect of *Bifidobacterium animalis* subsp. *lactis* SF on enhancing the tumor suppression of irinotecan by regulating the intestinal flora. *Pharmacol Res* 184: 106406.
131. Karami P, Abediankenari S, Goli H, Gholami M, Ahanjan M, et al. (2019) Evaluation of Cell Growth Inhibition of *Bifidobacterium Bifidum* Cell-free Supernatant Extract on 4T1 Tumor Cell Lineage. *Research in Molecular Medicine* 7: 1-6.
132. Liu S, Wicha MS. (2010) Targeting breast cancer stem cells. *Journal of clinical oncology* 28: 4006-12.
133. Liu H, Ma X, Yang X, Xiao S, Ouyang S, et al. (2025) *E. coli* Nissle 1917 improves gut microbiota composition and serum metabolites to counteract atherosclerosis via the homocitrulline/Caspase 1/NLRP3/GSDMD axis. *International Journal of Medical Microbiology* 318: 151642.
134. Sougioultzis S, Simeonidis S, Bhaskar KR, Chen X, Anton PM, et al. (2006) *Saccharomyces boulardii* produces a soluble anti-inflammatory factor that inhibits NF- κ B-mediated IL-8 gene expression. *Biochemical and Biophysical Research Communications* 343: 69-76.
135. Shenderov BA. (2013) Metabiotics: novel idea or natural development of probiotic conception. *Microb Ecol Health Dis* 12: 24.
136. Thoda C, Touraki M. (2025) Molecular Mechanisms of Probiotic Action Against Gastro-intestinal Cancers. *Int J Mol Sci* 26: 7857.
137. Hwang J, Yadav D, Lee PC, Jin JO. (2022) Immunomodulatory effects of polysaccharides from marine algae for treating cancer, infectious disease, and inflammation. *Phytotherapy Research* 36: 761-777.
138. Xin Z, Zhang M, Cui H, Ding X, Zhang T, et al. (2023) Algae: a robust living material against cancer. *International Journal of Nanomedicine* 18: 5243-5264.
139. Saadaoui I, Rasheed R, Abdulrahman N, Bounnit T, Cherif M, et al. (2020) Algae-derived bioactive compounds with anti-lung cancer potential. *Marine drugs* 18: 197.

140. Minhas LA, Kaleem M, Farooqi HMU, Kausar F, Waqar R, et al. (2024) Algae derived bioactive compounds as potential nutraceuticals for cancer therapy: A comprehensive review. *Algal Research* 78:103396.
141. Corso CR, Mulinari Turin de Oliveira N, Moura Cordeiro L, Sauruk da Silva K, da Silva Soczek SH, et al. (2021) Polysaccharides with antitumor effect in breast cancer: a systematic review of non-clinical studies. *Nutrients* 13: 2008.
142. Erfani N, Nazemosadat Z, Moein M. (2015) Cytotoxic activity of ten algae from the Persian Gulf and Oman Sea on human breast cancer cell lines; MDA-MB-231, MCF-7, and T-47D. *Pharmacognosy Research* 7:133.
143. Yao W, Qiu H-M, Cheong K-L, Zhong S. (2022) Advances in anti-cancer effects and underlying mechanisms of marine algae polysaccharides. *Int J Biol Macromol* 221: 472-485.
144. Srinivasan R, Chaitanyakumar A, Mageswari A, Gomathi A, Kumar JP, et al. (2017) Oral administration of lyophilized *Dunaliella salina*, a carotenoid-rich marine alga, reduces tumor progression in mammary cancer induced rats. *Food & function* 8: 4517-4527.
145. de la Mare J-A, Sterrenberg JN, Sukhthankar MG, Chiwakata MT, Beukes DR, et al. (2013) Assessment of potential anti-cancer stem cell activity of marine algal compounds using an in vitro mammosphere assay. *Cancer Cell International* 13: 1-14.
146. Moussavou G, Kwak DH, Obiang-Obonou BW, Ogandaga Maranguy CA, Dinzouna-Boutamba S-D, et al. (2014) Anticancer effects of different seaweeds on human colon and breast cancers. *Marine drugs* 12: 4898-911.
147. Lau T-Y, Kwan H-Y. (2022) Fucoxanthin is a potential therapeutic agent for the treatment of breast cancer. *Marine Drugs* 20: 370.
148. Etman SM, Elnaggar YS, Abdallah OY. (2020) Fucoindan, a natural biopolymer in cancer combating: From edible algae to nanocarrier tailoring. *International journal of biological macromolecules* 147: 799-808.
149. Rahmati S, Alizadeh M, Mirzapour P, Miller A, Rezakhani L, et al. (2023) The effect of marine algae derived exosomes on breast cancer cells: Hypothesis on a new treatment for cancer. *Journal of Cancer Research and Therapeutics* 19: 218-220.
150. Lamberti M, Zappavigna S, Sannolo N, Porto S, Caraglia M, et al. (2014) Advantages and risks of nanotechnologies in cancer patients and occupationally exposed workers. *Expert opinion on drug delivery* 11: 1087-101.
151. García-Aranda M, Redondo M. (2019) Immunotherapy: a challenge of breast cancer treatment. *Cancers* 11: 1822.
152. Liang Y, Zhang H, Song X, Yang Q (2020) Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. *Semin Cancer Biol* 60: 14-27.
153. Sampsell K, Hao D, Reimer RA (2020) The gut microbiota: a potential gateway to improved health outcomes in breast cancer treatment and survivorship. *International Journal of Molecular Sciences* 21: 9239.
154. Xiong Y, Rao Y, Hu J, Luo Z, Chen C, et al. (2023) Nanoparticle Based Photothermal Therapy for Breast Cancer Noninvasive Treatment. *Adv Mater* 37: e2305140.
155. Gholikhani T, Kumar S, Valizadeh H, Mahdinloo S, Adibkia K, et al. (2022) Advances in Aptamers Based Applications in Breast Cancer: Drug Delivery, Therapeutics, and Diagnostics. *Int J Mol Sci* 23: 14475.
156. Mao XD, Wei X, Xu T, Li TP, Liu KS, et al. (2022) Research progress in breast cancer stem cells: characterization and future perspectives. *Am J Cancer Res* 12: 3208-3222.
157. Xue D, Lu S, Zhang H, Zhang L, Dai Z, et al. (2023) Induced pluripotent stem cell derived engineered T cells, natural killer cells, macrophages, and dendritic cells in immunotherapy. *Trends Biotechnol* 41: 907-922.
158. Wang Y, Minden A. (2022) Current molecular combination therapies used for the treatment of breast cancer. *International journal of molecular sciences* 23:11046.
159. Meng Z, Ye Z, Zhu P, Zhu J, Fang S, et al. (2022) New developments and opportunities of microbiota in treating breast cancers. *Frontiers in Microbiology* 13: 818793.
160. Wu H, Ganguly S, Tollefsbol TO (2022) Modulating microbiota as a new strategy for breast cancer prevention and treatment. *Microorganisms* 10: 1727.
161. Górka A, Przystupski D, Niemczura MJ, Kulbacka J. (2019) Probiotic bacteria: a promising tool in cancer prevention and therapy. *Current microbiology* 76: 939-949.
162. de Moreno de LeBlanc A, Matar C, LeBlanc N, Perdigón G (2005) Effects of milk fermented by *Lactobacillus helveticus* R389 on a murine breast cancer model. *Breast Cancer Res* 7: R477-86.